Indian Heart Journal – A Clarion Call

Dear Colleagues,

It is with a great sense of pride that I present to you the first issue of the Indian Heart Journal of the new millennium. Over the last 50 years, the Indian Heart Journal, the voice of the Cardiological Society of India, has achieved a distinctive place of its own. This has been possible due to the hard work and collaborative efforts of its members, and also due to the vision and wisdom of my predecessors. I feel greatly honored and humbled in taking over as the editor of the Indian Heart Journal, following those stalwarts. While I am delighted to assume this onerous responsibility, I have a sense of trepidation when I look at the achievements of the past and the daunting task ahead. It will be my endeavor to strive and maintain the academic excellence of the Journal. Towards this end, I shall always look forward to your inputs and advice.

We are fortunate to live in an era of tremendous advances in knowledge, particularly in the field of cardiology. This gives us unprecedented opportunities in patient care, but also poses the challenge of keeping ourselves updated with recent advances, so as to provide optimal medical care to our patients. The need for a medium that provides continuous medical education, serves as a platform for exchange of ideas and research, and provides a perspective and direction to the contemporary knowledge is perhaps more than ever before. The Indian Heart Journal is well-poised to serve this pivotal role by virtue of its mandate, and because of the will and commitment of its contributors. Education and dissemination of core information through the medium of the Indian Heart Journal will continue to remain our top priority. Various amendments and efforts in this direction will be evident gradually.

It is my belief that the Indian Heart Journal must particularly focus on the problems and prospects of Indian cardiology. The magnitude of the cardiovascular disease burden in India is stupendous. While we are still besieged with the burden of rheumatic heart disease, the epidemic of coronary artery disease is not round the corner anymore, but bang in the middle of our lives. Thus, the double burden of “modern” and “not so modern” diseases is a cruel reality like the recent earthquake that shook parts of our country. With our poor level of socioeconomic development and health infrastructure, a routine lukewarm response to the challenge of cardiovascular diseases would not be enough. We need innovative research and ways of solving our problems. Such research, yielding context-specific solutions in one developing country, will be more relevant to others in a similar health care system than research from developed nations. Indian research in cardiology, therefore, now has a unique opportunity to influence the practice of cardiology in large parts of the world. The Indian Heart Journal will seek to play its role by becoming a vehicle for publication of high quality research with outreach in application and impact. While a journal merely publishes research, I wish and pray that research on preventive cardiological issues, on cost-containing measures, and on rheumatic heart disease gain momentum, so that we are relevant to our society.

Friends, a lot has been achieved but much more remains to be done. If you put your best foot forward for the Indian Heart Journal, I am sure that we can make a higher impact on the international arena. We will continuously strive to make the Journal more readable. Please do not hesitate to communicate your ideas, comments and criticism for improving the Journal to me personally. We have started a new section on cardiovascular images and request you to send photographs of Chest X-ray, ECG or any other material of...
educational value. The section on recent trials would be coupled with expert comments. A section on current perspective, where eminent professionals in the field will express their opinion on matters such as policy, education and research is also envisaged.

An unbiased, quick, high quality peer-review process remains the backbone of any Journal. Much of the delay in publishing relates to the delay during the review process. I seek your cooperation in this process, even as we try to expedite the procedure. With advances in information technology, the time lag should be reduced further. Gradually, we shall move towards electronic submission of manuscripts. The Journal is now available online at www.indianheartjournal.org.

Through the editorial column of the Indian Heart Journal, I wish to thank the authors of review articles and the reviewers of manuscripts submitted to the Journal. I cannot overemphasize the fact that it is through their selfless contributions and due to their academic spirit that a journal derives its sustenance. I also thank all the editorial consultants of various subdisciplines for their willingness to help. I am grateful to my departmental colleagues for their unreserved help and support. I also appreciate the generous fiscal support from the industry.

Finally, I thank you once again for reposing the confidence in me and look forward to a fruitful and continuing interaction in the future.

With Best Wishes,

(VK BAHL)
The 20th century was distinguished by the identification of group A streptococcal (GAS) pharyngitis as the cause of acute rheumatic fever (ARF), and by the demonstration that both primary and secondary attacks of ARF are preventable by the appropriate use of penicillin to treat and prevent these infections. Notwithstanding these brilliant achievements, ARF and rheumatic heart disease (RHD) remain major public health problems throughout the developing countries of the world, that is to say, in most of the world's population. Moreover, the spectacular decline in ARF and RHD in developed countries cannot be attributed to penicillin therapy alone. The decline in ARF began well before the widespread use of penicillin and was coincident with improved living conditions, especially better housing.

Moreover, in the face of the virtual disappearance of ARF in developed countries, GAS is still identified in up to 25% or more of throat cultures made in schoolchildren with pharyngitis. Although many of these positive throat cultures may represent carriage of GAS rather than true infection, a significant number, if not most, have been documented immunologically as actual infections. Obviously, these sporadic streptococcal sore throats are not of the same rheumatogenic potential as those that caused military ARF epidemics with attack rates as high as 3% or more in patients with untreated GAS pharyngitis (see below). If the GAS pharyngitis currently encountered in schoolchildren of developed countries were rheumatogenic, treatment of GAS pharyngitis alone would not have accounted for the decline in ARF because most patients with sore throats do not present themselves for treatment, and those who do so do not now regularly receive or complete the rigorous regimens required for preventing the disease.

So, why did ARF virtually disappear during the 1960s and 1970s when GAS pharyngitis did not? And why did it reappear in the 1980s in focal outbreaks at both US military bases and in civilian populations and then subside again without apparent change in the incidence of GAS throat infection? And in these focal outbreaks, why did ARF affect middle-class populations who had no apparent deficit in health care? To help explain these observations, one needs to appreciate the fact that the great array of clinical syndromes produced by GAS, and the secular fluctuations in their epidemiology speak for remarkable diversity of strains found within what we have classified taxonomically as a single species.

Current concepts of the pathogenesis of ARF: Although the pathogenesis of ARF remains obscure, certain requirements for its development have been well established.1

The site of infection must be pharyngeal.2 Regardless of how virulent an invasive strain may be, ARF does not result when it is introduced extra-pharyngeally, e.g. through skin lesions or wound infections, or from puerperal sepsis.

Moreover, to cause ARF, GAS pharyngitis also requires certain conditions. Throat carriage alone is not causative.2 An immune response is required and even in rheumatogenic infections, the attack rate of ARF varies directly with the intensity of the immune response.3 Thus, there seems to be a quantitative factor related to the magnitude of antigen stimulation. Although a precise pathogenetic "rheumatogenic" factor has not been identified, all GAS strains that have been clearly shown to produce ARF by prospective studies have similar virulence characteristics.

GAS virulence: GAS is a natural pathogen only for human beings. Whereas all members of the species are identified by their group-specific carbohydrate cell wall, its outer surface is composed of tiny hair-like coiled projections by which the organism adheres to tissues4 (Fig. 1). In virulent strains, these structures contain an extractable and remarkably heterotypic antigen, the M protein.5 More than 100 immunologically specific M serotypes have so far been identified. Immunity to virulent GAS infection is only M type-specific, accounting for the frequency of GAS infections. When fully virulent, each chain of cocci is surrounded by a capsule of hyaluronic acid that is responsible for the "mucoid" appearance of GAS colonies on blood agar (Fig. 2). The larger the capsule, the smaller the chains (Fig. 3). The capsule is produced only during active growth of the organism. Streptococcal hyaluronate is chemically identical to that occurring ubiquitously in human connective tissues so that antibodies to it are not readily raised. Thus, anti-capsular immunity does not occur.

Correspondence: Professor Gene H. Stollerman, # 21, The Courtyard, Hanover, New Hampshire 03755, USA, e-mail: gstollerman@valley.net
and the host defense to virulent strains depends on anti-M antibodies.

Both components, M protein and capsule, are primarily responsible for the striking resistance of virulent strains of GAS to phagocytosis. But M protein and capsule are rapidly lost during convalescence from acute pharyngitis, or shortly after leaving the host, when landing on fomites, or when grown in artificial media. After fresh isolation, strain virulence may be maintained, however, by frequent transfer through fresh human blood or by intraperitoneal mouse passage. Once host defenses are penetrated, strains of GAS excrete many extracellular toxic substances that enhance tissue destruction and promote invasion (streptolysin S and O, streptokinase, DNA nucleases, hyaluronidase, erythrogenic toxins, anticomplementary proteins, etc.).

On blood agar cultures, clones of encapsulated variants form large "mucoid" colonies resembling a drop of oil, whereas loss of encapsulation results in colonies that are opaque and "pearly" in appearance (Figs 2a and b). Considering the potential significance of this observation epidemiologically, it is surprising how infrequently clinical microbiology laboratories recognize and report the presence of mucoid colonies on throat cultures. In the past, their appearance in throat cultures from military cohorts who were under prospective surveillance regularly predicted severe epidemics of streptococcal pharyngitis and rheumatic fever (RF). Many years ago, my colleagues and I demonstrated that even antibody-free germ-free mice readily destroyed GAS clones lacking M protein and hyaluronate capsules.
Throat carriage, however, may sometimes stubbornly persist during convalescence when strains have lost these virulence factors. Such persisters may retain mucosal adherence ligands, such as surface lipoteichoic acid \(^1\) and F proteins \(^1\) that stimulate internalization of the organisms by epithelial cells. \(^1\) Such internalization is actually inhibited by the hyaluronate capsule \(^1\), \(^2\) whose genetic expression is associated with that of other virulence factors (e.g. M protein, streptolysins and erythrogenic toxins), causing cellular injury and promoting the invasion of deeper tissues. \(^1\)–\(^3\)

Thus, the human throat is readily colonized by a variety of GAS strains of varying virulence, accounting for a spectrum of infection ranging from an asymptomatic colonization to local inflammation and extension to deeper tissues. Confirmation of the diagnosis of actual streptococcal pharyngitis therefore requires more than positive cultures—a significant increase in the titer of streptococcal antibodies (e.g. antistreptolysin O, anti-DnaseB, etc.).

**Evolution of the concept of rheumatogenic strains:**

The World War II epidemics of RF that occurred among military recruits, assembled from many different areas of the US, were shown to be caused by GAS strains belonging to but a few prominent M serotypes. \(^1\)–\(^3\) These epidemic strains were heavily encapsulated, M protein-rich variants. When introduced into the ranks of close-living recruits, they spread rapidly, not by fomites but by droplet infection through close person-to-person contact. Infections by strains representing several M serotypes were associated with a strikingly similar post-infection ARF attack rate of approximately 3% in untreated individuals. \(^4\) This attack rate varied with the intensity of the immune response. \(^1\)

In subsequent studies in the 1950s, it became clear, however, that common sporadic GAS sore throats in US schoolchildren were associated with little or no RF. \(^5\) Indeed, subsequent literature searches confirmed that GAS strains within but a limited number of M serotypes had actually been associated with previous well-studied military epidemics of ARF. In the civilian population of schoolchildren the "mucoid" GAS strains belonging to these M types seemed to have virtually disappeared. \(^1\), \(^5\)

**Non-rheumatogenic GAS:** As early as the late 1930s, Alvin Coburn noted that ARF was not reactivated by throat infections due to strains representing certain M-protein serotypes. \(^5\) By the 1950s, it was further reported that strains within certain M types caused acute glomerulonephritis (AGN) \(^6\) rather than ARF, the two complications very rarely occurring from the same antecedent infection. By the 1960s, GAS strains causing streptococcal pyoderma (impetigo), a primary skin infection, were shown to be different from those primarily infecting the throat. Some pyoderma strains caused AGN, but none caused ARF. \(^7\)–\(^9\) Therefore, the so-called "skin strains" must be regarded as non-rheumatogenic.

**Properties of known rheumatogenic strains:** Some characteristics of the GAS strains clearly responsible for the great ARF epidemics of World War II have been defined. \(^1\)

Briefly, they are very rich in M-protein (i.e. have very large M molecules), are heavily encapsulated, and are highly mouse-virulent. They produce striking "mucoid" colonies on blood agar plates. They are tropic primarily for the throat rather than the skin, infecting the latter only secondarily through wounds or skin lesions. They evoke strong type-specific immune responses in humans and in mice, much more so than M type-specific responses from pyoderma strains. They do not contain the lipoproteinase commonly found in skin strains (serum opacity factor). They have been found so far to be distributed among a limited number of serotypes, such as M 1, 3, 5, 6, 18, 19 and 24, and some others. \(^10\)

It should be emphasized, however, that the M serotype alone does not equate with rheumatogenicity because strain variation is common within a given serotype. This fact has caused confusion and controversy about the concept of rheumatogenic M serotypes. On the other hand, very few studies have routinely assessed encapsulation and many strains identified as M-positive may have relatively small or no capsules.

**Why are rheumatogenic strains difficult to identify?**

In a severe epidemic of GAS pharyngitis, one strain of a given M serotype often becomes prevalent. In such cases, the attack rate of ARF following such specific infections can be accurately calculated. In clinical practice, however, by the time rheumatic fever is diagnosed the infecting strain is usually not recoverable, or the clones persisting in the patient's throat may have attenuated so that their M type may no longer be recognizable. Moreover, new GAS strains may have been acquired during the latent period between the antecedent infection and the onset of ARF.

ARF patients are often referred to centers (especially pediatric cardiology clinics) where in-depth studies of streptococcal strains are not usually made. Reference laboratories often receive strains that dissociate during transfer and no longer express all the virulence factors. When clinical laboratories make throat cultures, colony morphology is rarely observed or reported. Yet the appearance of mucoid colonies in a cohort may signal
danger. For example, in the late 1950s, in a prospective surveillance of throat cultures from naval recruits of the Great Lakes Naval Training Center, Great Lakes, Illinois, the sudden appearance of a predominant highly "mucoid" M type accurately predicted the onset of a severe epidemic of ARF.

Disappearance and reappearance of rheumatogenic strains in the USA: The disappearance of the notorious rheumatogenic M types from a population of Chicago schoolchildren was an observation made by my colleagues and myself several decades ago. In the 1980s, however, an outbreak of ARF reappeared at the San Diego Naval Base, at Fort Leonard Wood, Missouri, and among schoolchildren in several other regions of the United States, most notably in Utah and the Rocky Mountain area. In these regions, investigating teams of the USPHS's Centers for Disease Control discovered that the mucoid, rheumatogenic strains belonging to the notorious M types of the past were seeded among contacts of index cases of ARF. This outbreak has included more than 500 cases since then in the Salt Lake City area alone. Moreover, the outbreak occurred among middle-class Caucasian children with no risk factors other than perhaps household crowding.

Obviously, identification of rheumatogenic and other specifically pathogenetic strains requires prospective studies of GAS pharyngitis by clinical investigators, knowledgeable about the microbiology of the GAS, its epidemiology, and its clinical sequelae. Unfortunately, in many areas of the world where ARF still rages, a search for local rheumatogenic strains has not been systematically conducted. In populations where rampant pyoderma coexists with a high incidence of ARF in the same cohorts, such as among the aborigines of the Northern Australian territories, and where efforts at strain identification have been made, investigators understandably have found it difficult to sort out the throat strains causing ARF from pyoderma strains. Pyoderma strains are notoriously transmissible from skin lesions to the throat, where they may persist, resulting in a confusing array of carried strains.

In Trinidad, however, where extensive impetigo, acute glomerulonephritis (AGN) and ARF once coexisted closely, painstaking studies revealed that strains colonizing the skin, although periodically causing an epidemic of AGN, were not associated with concordant increase in the prevalence of ARF on the island. In Memphis, Tennessee, a southern city of the US, the seasonal separation of pyoderma and AGN in the summer and ARF in the late fall and winter further demonstrated the inability of skin strains to cause ARF. In the colder months, however, the precise strains causing ARF could not be identified for reasons noted above.

The molecular biology and genetics of well-known rheumatogenic GAS: By the 1980s, the primary molecular structure of M protein was determined and its type-specific antigen was shown to reside in its small terminal N-acetyl peptide. Two highly conserved epitopes within M protein divide GAS immunologically into Class I (throat) and Class II (skin) strains. All RF strains fall clearly into Class I throat strains and individuals who had contracted RF were shown to have higher titers against the Class I epitope, whereas they lacked antibodies to the Class II epitope. Moreover, in the large M protein molecules of Class I rheumatogenic strains, distinct epitopes were identified that cross-react with cardiac, synovial, and brain tissues and these were separable from the terminal type-specific antigen.

The genes of M protein (een) have now been shown to be divided into four subfamilies of nucleotide sequences, arranged in five distinctive chromosomal patterns, identified as A–E. By these genetic patterns, rheumatogenic pharyngitis strains are clearly differentiated from impetigo strains, but not yet clearly from all other throat strains. Whether epitopes that cross-react with host tissues are present exclusively in RF strains is not clear. An attractive hypothesis is that the deposition of a heavy antigenic load of these cross-reactive epitopes in pharyngeal lymphoid tissues, already hypersensitized during early childhood by repeated streptococcal infections, causes a break in the immune tolerance of susceptible hosts that leads to the various stigmata of RF.

Swallowing large amounts of such antigens seems to have a powerful immunizing effect. It is an old observation that streptococcal pharyngitis produces a more striking immune response to all streptococcal antigens in those who develop rheumatic fever compared to those who do not, whereas RF patients respond normally to other common test antigens. After nasal administration of synthetic M vaccines, mice produce type-specific IgA antibodies and are protected from experimental systemic challenge with homologous M-type strains. In addition, the adjuvant effect of the superantigenic properties of the proximal conserved part of the M protein (see below) may also promote exaggerated immune responses and autoimmunity.

Recently, the M protein genes and those of hyaluronic acid, streptolysin S, erythrogenic toxins, and others have been identified and now provide a genomic approach to characterizing GAS strains. Other than quantitative features...
of virulence as measured by M protein and hyaluronate content, however, molecular differences between rheumatogenic and non-rheumatogenic throat strains are not yet clear.

**Immunological theories of pathogenesis** have been recently reviewed exhaustively. Numerous streptococcal antigens have been shown to be cross-reactive with a variety of cardiac, brain and synovial tissues. The probable role of the immune system of the gut in regulating autoimmunity should be considered more seriously in the future since a heavy load of antigens and toxins are swallowed in the course of severe GAS pharyngitis and the GI route of entry is one that is bypassed by extrapharyngeal GAS infections that do not cause ARF. Moreover, autoimmunity may be controlled to a great extent by the immune system of the gut.

Nor has the role of many streptococcal toxins in ARF pathogenesis been excluded. For example, the membrane-destroying toxin, streptolysin S, whose expression is controlled by GAS virulence genes, may release some host intracellular antigens that may provoke cell-mediated autoimmunity. More than 50 years ago, streptolysin S was shown to be nonantigenic and therefore not neutralized in ARF patients despite their repeated GAS infections.

Recently, the valvular endothelium of patients with RHD who required valve replacement, has been found to be reactive with the adhesion molecules of CD4+ and CD8+ lymphocytes penetrating through the valvular subendothelial layers. Such an infiltration may represent an important cell-mediated autoimmune step in the pathogenesis of rheumatic valvulitis. The conserved, nontype-specific "superantigen" portion of the M molecule contains nontype-specific epitopes to which we become progressively hypersensitized by repeated childhood GAS infections. In genetically susceptible hosts, these heighten the immune responses to streptococcal antigens, as observed in ARF patients. Such immunologic stress may also break immune tolerance and may account for the variety of cross-reactive antibodies found in synovia, skin, brain and heart tissues of RF patients. Immune complexes may produce nondestructive synovitis of the joints in patients with ARF and nondestructive reactions in the basal ganglia observed in Sydenham's chorea, whereas cell-mediated autoimmune cytotoxic reactions may destroy heart valves. The varied clinical manifestations of ARF are therefore not unexpected.

**The rheumatic host:** The degree to which host factors are acquired or genetic is unclear. Both factors may be important. No race or ethnic group, however, is intrinsically resistant or unusually susceptible to ARF, but age and gender differences are sometimes apparent. ARF is very rare in young children before full maturation of the immune system reaches its peak by the end of the first decade and wanes with age thereafter. Carditis is most common and severe in the young and arthritis more common in adults. Sydenham's chorea, equally common in both sexes before puberty, is virtually non-existent in sexually mature males and is exacerbated in women by pregnancy. Also well recognized is a greater propensity in women to develop late-onset, tight mitral stenosis. Rheumatic recurrences tend to be mimetic, suggesting host predisposition. Isolated polyarthritis, chorea and carditis tend to recur independently, and susceptibility to all manifestations of rheumatic recurrences wanes with age. Host factors might also be expected to predispose to the chronicity of all rheumatic manifestations, especially valvulitis.

However, specific genetic susceptibility is unclear. ARF is less concordant in identical twins (about 20%) than it is in twins with other immunologic diseases such as atopic allergy and hyperthyroidism, or in infections such as tuberculosis or poliomyelitis. An association with the gene products of human haplotypes, so productive in many autoimmune disorders, has not been as clear in ARF. An increased frequency of HLA-DR4 and HLA-DR2 among White and Black patients with rheumatic heart disease has been noted. Other studies have implicated DR1 and DRW6 as susceptibility factors in South African Black rheumatic heart disease patients, and recently of DR7 and DW53 in Brazilian patients. These conflicting results have raised speculation that the observed associations might be of Class II genes close to, or in linkage disequilibrium with a putative RF susceptibility gene.
John Zabriskes and his colleagues have reported the frequent expression of a B cell alloantigen, unrelated to MHC, in diverse populations of RF individuals, principally those with rheumatic heart disease. A monoclonal antibody (DB/17) prepared by immunizing mice with B cells from an ARF patient is expressed on increased numbers of B cells in all rheumatic heart disease patients of diverse ethnic origins but in only 10% of normal individuals. This antigen shows no association or linkage to any of the known HLA haplotypes, nor does it appear to be related to B cell activation antigens. Its source and pathophysiologic role remains obscure. Obviously, it would be of considerable importance if it turns out to be a reliable marker of susceptibility of rheumatic heart disease at birth. It has not been adequately studied in ARF patients with isolated polyarthritis or chorea.

Prevention of rheumatic fever

The above discussion brings complexity to what is, on the face of it, a dismally simple fact: treatment and prevention of GAS pharyngitis prevents ARF. For the prevention of recurrences (secondary prophylaxis), rather than primary attacks (primary prevention), the issues are simpler because the susceptible rheumatic host is already identified. Current issues of secondary prophylaxis are therefore considered first.

Secondary prevention of rheumatic fever: For prevention of rheumatic recurrences, continuous antibiotic prophylaxis is now recommended by health authorities throughout the world. Monthly injection of benzathine penicillin G is, by far, the most stringent and effective regimen. In some populations with a high prevalence of ARF, however, some observers have reported that the last week of the month is not completely covered by this regimen and they choose to administer it every three weeks. One should be sure, in any case, that the commercial formulation of the drug contains the full dose of 1.2 million units of benzathine penicillin G and not the commonly marketed confusing formulations containing smaller amounts of benzathine penicillin G mixed with shorter-acting penicillin G compounds. Where ARF is no longer prevalent, oral penicillin V 600 000 units b.i.d. now suffice. For that matter, sulfadiazine, 0.5 g b.i.d. is also effective and inexpensive and thus useful for secondary (but not primary) prevention.

How long to continue these regimens is a matter of clinical judgement, recognizing the major variables that affect the decision: (i) how frequently RF occurs among cohorts, (ii) how recent and severe the rheumatic attack, (iii) the presence and severity of rheumatic heart disease. Penicillin prophylaxis has been safely suspended after several years of treatment when rheumatogenic streptococci have been shown to have disappeared from the community.

In a 5-year follow-up study that stratified recurrences by various risk factors, patients without rheumatic heart disease developed recurrences following GAS infections with attack rates that varied from 4% in patients with a small increase in ASO titer to 36% in those with a marked rise. The recurrent attack rate was, of course, much higher in patients with rheumatic heart disease where it may exceed 50% in those with the greatest immune responses. The duration of prophylaxis is therefore a variable to be decided by the local prevalence of ARF and the presence or absence of heart disease and its severity. For those individuals with RHD, including adults exposed to school-aged children, discontinuation of prophylaxis at any age may be hazardous. In the US, however, recommendations for discontinuing prophylaxis have become more permissive, especially for patients without RHD for whom prophylaxis is recommended "for 5 years or until age 21 years, whichever is longer". Obviously, recommendations for the US population may not apply to all cohorts in developing countries that require a recommendation formulated by their own expert committees.

Primary prophylaxis: Treatment of GAS pharyngitis is in a state of turmoil in developed countries and varies greatly depending on the local prevalence of ARF. On the one hand, the emergence of throat flora resistant to antibiotics (gratefully, not GAS, but particularly S. pneumoniae), is a consequence of overuse of antibiotics for the treatment of non-bacterial respiratory infections. On the other hand, fear of ARF has made some expert committees reluctant to compromise on the penicillin regimens that are required to prevent ARF following rheumatogenic GAS pharyngitis. There is little doubt that treatment of GAS pharyngitis with a single intramuscular injection of 1.2 million units of benzathine penicillin G is the most reliable way to prevent primary attacks of ARF, but it is now rarely prescribed in the US and other developed countries. For developing countries, however, effective as it may be, the problem of delivering injections for sore throats is also an overwhelmingly practical one. But wherever injections of benzathine penicillin G for GAS pharyngitis have been widespread, ARF has rapidly declined, not because all cases of GAS pharyngitis disappeared but probably because the most virulent clones of GAS were driven out of the population.

More convenient is the alternative treatment of 10 days...
of oral penicillin V 500,000 units twice daily, but compliance with the required full 10 days of therapy is at best uncertain. Avoiding overuse of penicillin therapy for the sore throats that are predominantly of viral etiology requires throat cultures or rapid antigen diagnostic tests (RADTs). The predictive value of such negative tests may reduce the use of antibiotics by about 80%. Whereas this strategy may be the most practical and cost-effective approach to primary prevention in developed countries, its widespread application to underprivileged and underserved populations of the world is problematic. Nonetheless, we are still dependent on penicillin therapy for primary prevention of ARF and it is reasonable to focus intensive therapy on cohorts in whom RHD is most prevalent, and where the greatest reservoirs of rheumatogenic GAS are stored. Perhaps their spread can at least be somewhat inhibited.

Streptococcal vaccines: We will probably not eradicate RF from the world without a GAS vaccine. Several investigators are approaching the problem. James Dale and associates, for example, have prepared a recombinant multivalent vaccine composed of the end-to-end combination of the type-specific epitopes representing many of the most common M serotypes in which rheumatogenic strains are usually found (Fig. 4). Trials of efficacy in humans are currently underway. Oral immunization with similar vaccines is also promising since an M type-specific IgA response to this route of immunization has been well demonstrated. Considering how much M antigen is swallowed in the course of a GAS sore throat, the oral route for production of protective IgA to type-specific M determinants (free of host cross-reacting antigens) may be the most effective one. And considering the great number of M serotypes, we must focus on those known to contain strains of greatest rheumatogenic potential.

**Diagnosis**

Some limitations to the modified Jones Criteria have been emphasized, and these criteria are, after all, useful only as general guidelines. For example, in contrast to arthritis, Sydenham’s chorea, the major manifestation with the longest latent period following the antecedent infection, may present without any other major or minor features of ARF—so-called “pure chorea”. Also, isolated asymptomatic acute carditis may first come to medical attention several months into or after the rheumatic attack. By then, antibody titers may have declined to normal levels and the minor manifestations of systemic inflammation (fever, ESR, C-reactive protein, etc.) may have abated.

Recurrent ARF in patients with pre-existing rheumatic valvular disease is particularly problematic in the absence of non-cardiac major manifestations (e.g. polyarthritis or chorea). When rheumatic valvular disease pre-exists, clear recognition of a new bout of carditis requires evidence of fresh cardiac injury such as pericarditis, acute cardiac enlargement and/or sudden congestive heart failure, or a newly detected murmur from a valve not previously affected. The Jones Criteria therefore, apply most readily to initial attacks, and more diagnostic latitude is needed to interpret recurrent carditis in patients with pre-existing rheumatic heart disease. The steps in the evolution of modifications of the Jones Criteria have been reviewed recently in detail.

Problems in the diagnosis of isolated polyarthritis and the place of so-called “post-streptococcal reactive arthritis” in the diagnosis of ARF has been discussed elsewhere in detail as has the diagnosis of isolated Sydenham’s chorea and its possible relation to the so-called post-infectious autoimmune neurological diseases (PANDAs). These diseases include tics, Tourette’s syndrome, and obsessive-compulsive behaviour, all of which have been observed in some patients during or after an attack of rheumatic chorea.

**Isolated Carditis:** Rheumatic carditis is almost always associated with valvulitis. Isolated myocarditis or pericarditis without valvulitis is rarely, if ever, due to ARF. So, the finding of valvular involvement is critical and is greatly aided by noninvasive imaging methods.

**Echocardiography (EC) and Doppler studies:** Most cases of rheumatic carditis are not severe enough to be symptomatic and the diagnosis of isolated carditis previously depended on auscultation alone. Eighty percent or more cases of mitral regurgitation that are detected by EC are also readily diagnosed by experienced physicians by auscultation alone. The remaining “subauscultatory” cases are those with the mildest degree of mitral or aortic regurgitation. If rheumatic in origin, more than 80% of these valvular lesions are likely to heal without scarring. Moreover, the sensitivity of EC may detect degrees of valvular...
regurgitation within the physiologic range, and not functionally significant, especially in children and in very thin, active individuals with highly elastic valve leaflets and rings.

Although EC, particularly accompanied by Doppler studies, offers greater sensitivity and specificity for the assessment of valvular regurgitation, it need not be considered essential for the diagnosis of RF by experienced primary care physicians, especially in settings where the disease is common and medical resources limited. Nonetheless, cardiologists proficient in echo-Doppler technology, now use this method routinely to distinguish abnormal from physiologic valve leaks more sensitively and accurately than is possible by auscultation alone. Despite the relatively good prognosis of "silent" rheumatic mitral regurgitation, EC does, indeed, provide an accurate assessment of the presence and severity of valvulitis, especially in an era when cardiac auscultation has been taught less extensively and is used with less confidence by young clinicians. In any case, it is doubtful that a powerful diagnostic tool such as EC will be neglected in the assessment of valvular disease wherever the instrument is available, and certainly where its expense may not be too great a concern.

In my view, whether or not subauscultatory mitral regurgitation should be accepted as the sole criterion of carditis in the absence of other major manifestations of RF remains an issue and dependent on the experience of the examining cardiologist. Whether or not the Jones Criteria should be modified to incorporate these newer techniques is being debated by expert committees. Differences of opinion are tempered by considerations of the availability and cost–benefit of EC to developing countries, since the outcome of treatment and management of such minimal valvular inflammation may not differ significantly, whether they are detected or not.60

Right ventricular endomyocardial biopsy: When the characteristic murmurs of rheumatic carditis are detected early in the course of a rheumatic attack and are associated with other major manifestations of ARF, such as arthritis and fever, the yield of useful additional clinical information from endomyocardial biopsy (EB) is low. Its diagnostic sensitivity in one relatively large study was only 27%. Endomyocardial biopsy has, however, confirmed the presence of underlying carditis in unexplained congestive heart failure of acute onset in some patients with pre-existing rheumatic heart disease and elevated antistreptolysin titers, suggesting a rheumatic recurrence. In patients with chronic rheumatic heart disease, however, EB does not appear to provide additional diagnostic information. In my opinion, in patients with rheumatic carditis, EB should be limited to clinical investigation.

Treatment

Treatment has not changed much in recent decades.1 Because valvular scarring is suspected to be the result of cytotoxic cellular autoimmunity, anti-TNF drugs that seem to delay or reduce joint destruction in rheumatoid synovitis possibly might reduce valvular scarring in rheumatic carditis. However, there is no longer much argument, that corticosteroids, though symptomatically beneficial, do not prevent valvular damage.60 The new COX-2 inhibiting NSAIDs, though currently expensive, may be welcome as they reduce the adverse gastrointestinal effects of large doses of aspirin, although for four- to six-week therapeutic courses, such side-effects have not been a great problem, especially in children.

For mild rheumatic carditis, lingering doubt in the minds of some investigators about the possible long-term benefit of corticosteroids over salicylates was based upon the results of a few studies suggesting a favorable outcome of such treatment for minimal rheumatic mitral regurgitation.68 These minimal mitral murmurs are most difficult to standardize (perhaps EC will help) but spontaneous healing occurs in 80% or more of patients with ARF, so that the putative advantages of corticosteroids for these mild cases of carditis are not likely to be resolved. For the present, most physicians choose to use corticosteroids over salicylates in rheumatic carditis simply because they are more potent anti-inflammatory agents, a practice many authorities do not endorse except in patients with severe carditis with congestive heart failure for whom the powerful suppression of inflammation may at times make management easier by suppressing fever and reducing toxicity and anemia.1

Summary and conclusions

In the latter half of the 20th century, the clinical importance of variation in the virulence of strains of GAS has been clearly demonstrated. Although still obscure, the pathogenesis of ARF requires immunologically significant infection of the throat by virulent GAS strains. These strains contain large hyaluronate capsules and large M-protein molecules. The latter contain epitopes cross-reactive with host tissues, and also contain superantigenic toxic moieties. In areas where ARF has become rare, GAS pharyngitis continues to be common but is caused predominantly by GAS strains of relatively low virulence. These, however, may
colonize the throat avidly and stubbornly. Molecularly distinct pyoderma strains may cause acute glomerulonephritis, but they are not rheumatogenic even though they may secondarily infect the throat. In developing countries, with a very high incidence of rheumatic heart disease, identification of the prevalent rheumatogenic GAS strains and development of a multivalent vaccine against them is currently an interesting strategy. Pending vaccine development, intense primary and secondary penicillin prophylaxis should continue to be sharply focused on populations with the highest prevalence of RHD as such measures may often succeed in driving away the most virulent rheumatogenic clones of GAS from their midst.

References

2. Wannamaker LW. The chain that links the heart to the throat. Circulation 1973; 48: 9–11
5. Lancefield RC. Specific relationship of cell composition to biological activity of hemolytic streptococci. Harvey Lectures 1940–1941 1941; 35: 251
10. Frank PF, Stollerman GH, Miller LF. Protection of a military population from rheumatic fever. JAMA 1965; 193: 775–83
20. Stollerman GH, Siegel, AC, Johnson EE. Variable epidemiology of streptococcal disease and the changing pattern of rheumatic fever. Modern Concepts of Cardiovascular Disease 1965; 34: 45–48
32. Centers for Disease Control: Acute rheumatic fever—Utah. MMWR 1987; 36: 108


42. Stollerman GH, Bernheimer AW. Inhibition of streptolysin S by the serum of patients with rheumatic fever and acute streptococcal pharyngitis. J Clin Invest 1950; 29: 1147–1155


64. Minich LL, Tani LY, Pagotto LT, Shaddy RE, Veasy LG, Doppler echocardiography distinguishes between physiologic and pathologic "silent" mitral regurgitation in patients with rheumatic fever. Circ Cardiol 1997; 20: 924–926

65. Veasy LG. Echocardiography for diagnosis and management of rheumatic fever. JAMA 1993; 269: 2084


Rheumatic Fever and Rheumatic Heart Disease in India at the Turn of the Century

S Padmavati
Director, National Heart Institute, New Delhi, India

A high incidence of rheumatic fever and rheumatic heart disease was prevalent in the UK, USA and in the Western Europe at the end of the nineteenth and in the early years of the twentieth century. Today, it seems possible to survey this problem over the last century. The earliest reference in India was in 1910, stressing the low prevalence of rheumatic heart disease (RHD) in autopsies. A similar view was expressed by some British military physicians about the clinical cases. However, by 1938 a high prevalence was noted and publications after World War II from all parts of India pointed to RHD being the most common form of heart disease, accounting for nearly 40% of cardiac cases seen in hospitals.1

Earlier, the prevalence of RHD was assessed from several sources (Registrar General, population surveys, school surveys, autopsy and hospital admissions). Today school surveys appear to be the most informative source. With echocardiogram and other diagnostic aids, it is possible to assess fairly accurately the prevalence of RHD, while the prevalence of rheumatic fever (RF) is unclear as the symptoms are vague or mild. Between 1940 and 1983, school surveys estimated the average prevalence of RHD to be between 1.8 and 11 per 1000 in schoolchildren (average 6 per 1000), while from 1984 to 1995, the prevalence was reported to be from 1 to 3.9 per 1000. The incidence of acute RF, a less clear entity, was 0.05 to 1.7 per 1000 in the first period and 0.18 to 0.3 per thousand in the second period. However, the data are not comparable as the groups surveyed in the second period were small. For these reasons, conclusions regarding a decline are not warranted.2

Recent Data

Recent reports, however, point to a high prevalence of RHD, as judged from the young age of children observed to be suffering from the disease in school surveys, and at pediatric clinics, and from juvenile patients coming for balloon mitral valvotomy (BMV).

Thus in Delhi,3 in 1999, out of 191 children below 12 years of age with definite acute RF, 7.9% were below 5 years, 31.4% between 5 and 9 years and 60% above 9 years. The male–female (MF) ratio was 1.5:1. In 378 patients from Orissa4 below 19 years, the mean age was 15.1±4.4 years. The MF ratio was 4:1. Mild mitral stenosis (MS) was present in 34.9% and severe MS in 33%. In 77 patients with rheumatic chorea from Kerala,5 the age ranged from 4.5 to 18 years, the mean being 9.3 years, the MF ratio was 1.6:1, and 1.57% had a mitral valve involvement. In 2000, in a school survey involving 3963 children from the district of Kanpur, the prevalence of RHD was 4.54 per 1000 (urban 2.56 and rural 7.42). The prevalence of RF was 0.75 per 1000 (rural 1.20, urban 0.42). Cases of RHD were distributed equally between the ages of 7 to 11 and 12 to 15 years. The MF ratio was 1:0.8.6 In one series of 155 consecutive children below 12 years, the age range was 9.3±2.1 years and the MF ratio 1:0.6.7

These recent data suggest that a large number of cases of RHD are still seen frequently in young children. There is also no predominance of the female sex. It is not just old cases coming to the hospital for treatment, e.g. congestive heart failure (CHF), BMV, closed mitral commissurotomy (CMV) or surgery. It must be pointed out that the prevalence of RHD in western countries is below 0.5 per 1000 and below 1 per 1000 for RF in primary schoolchildren.2

Balloon mitral valvotomy: Indications for BMV are rapidly expanding. BMV is being performed not only in young adults but also in young children with acute RF (age 10.9±9.2 years).8 BMV is also being carried out in young pregnant women,9,10 and is increasing in popularity as compared to CMV11 because of the short hospital stay and lack of a scar. Even the prohibitive cost of the Inoue balloon has been met by the reuse of the balloon 3 or 4 times. Although such a reuse of catheters has been frowned upon abroad,12 the Cardiological Society of India has issued specific instructions for it.13 Open mitral commissurotomy (OMV), mitral valve replacement (MVR) and MV repair are beyond the capacity of most of the poor Indians who suffer from the disease. BMV is now practised in many centers, mostly in government hospitals in the major metros where cases of rheumatic mitral stenosis are in
plenty. Refinement of the technique such as the use of metallic commissurotomy is being reported with initial success.14

**Hospital admissions:** Patients of RHD are usually admitted for an acute exacerbation of RF, for treatment of CHF or for BMV or surgery. With centers for cardiac interventions sprouting all over the country, the number of cases in a particular center may rise or fall according to the purpose of admission. Thus data from CMC, Vellore showed a fall between 1960 and 1989,15 while no such reliable data are available from other hospitals. Death certificates are also not reliable sources of data, and autopsies are almost unavailable in India at present.

**Prevention**

There are 3 main methods used in prevention as given below:

**Primary and secondary prophylaxis:** The Indian Council of Medical Research (ICMR) projects on primary, secondary and seasonal prophylaxis have shown the efficacy of these methods.1 Further it has been shown that these can effectively be given through the regular health care systems of the country, viz. Primary Health Centres (PHC)16 and School Health Services (SHS)17 and through General Practitioners (GP). The SHS system is better than the PHCs.

Secondary prophylaxis remains the cornerstone of prevention. Primary prophylaxis is more difficult as it has to be given for all cases of sore throat as streptococcal isolation before treatment is near impossible.

However, no nationwide program exists, due to lack of political will.

**Public health education:** While the government was seized of the magnitude of the problem as early as 1966, and the control of RF was included in the Fourth Five-year Plan, it has not figured in any of the subsequent Plans.

The ICMR has had 6 nationwide research projects on RF/RHD (1966–1990) and two "transfers of technology" in 1987 and 1993. However, due to the lack of involvement of Central and State Governments these programs have not become widespread. Videos in English and local languages have been made by the ICMR and the All India Heart Foundation (AIHF) and made available on the national network and to interested groups.

There is no doubt, thanks to these efforts, that there is now awareness of RHD throughout the country and injections and tablets of penicillin are being given freely to children, both for primary and secondary prophylaxis. However, the government order banning penicillin injection in government hospitals in some Indian states still exists. Much more needs to be done, particularly in the underdeveloped and troubled parts of the country and in areas with low literacy like the states of Bihar, Madhya Pradesh, Uttar Pradesh, the North East, and Jammu and Kashmir. The two "transfers of technology" were not enough for this vast country and need to be repeated over many sessions jointly by the Central and State Government.

**RF vaccine:** With the availability of new technology18 and thanks to the advances in molecular biology, the vaccine is now a distinct possibility. The ICMR has been actively involved in setting up research for an RF vaccine. It has initiated the Jai Vigyan Mission Mode Project at Chandigarh and Vellore wherein studies have already been initiated on the development of such a vaccine. It has proposed to undertake vaccine development using Indian strains. Collection of strains is being done through the sub-study on the epidemiology of group A streptococci and a study on preparedness for primary prophylaxis using the vaccine would be undertaken.

The ICMR has also initiated RF registries for secondary prophylaxis at these centers and will extend them to other regional centers through a network of satellite centers to cover the entire country (DG, ICMR, personal communication).

**Epilogue**

Some researchers believe that RF and RHD are getting milder the world over. However, more evidence for this is needed.

While in recent years some countries have reported a milder form of the disease, the findings from others are the reverse. India, Thailand and Sri Lanka were identified for support in South-East Asia for secondary prevention after the ad hoc committee on RF and RHD was set up by the ISFC in 1982. The results, however, are not evident. The project at Chandigarh is functioning. There is a decline in RHD reported from Thailand, but the incidence in the Middle East (Lebanon) is high.19

One hundred years is a long time for a disease of infectious origin to continue its ravage unabated. Although RF has now almost disappeared from the West, it can recur as it did in the USA in 1987. It continues to kill and maim the population in the developing countries of Asia, Africa and South America. Whether it will vanish or not in the new millennium due to change in the virulence of the streptococcus or the new vaccine on the horizon is yet to be seen.
The big question is—has there been a significant decline in RF and RHD in India? Can we now ignore the problem? The answer is definitely no. The evidence points to many children and young adults being affected in several parts of the country. Overpopulation, poverty, illiteracy, overcrowding and lack of access to medical care are all responsible for the continuing high incidence. Hospitals in both the private and public sectors are swamped by a large number of admissions for coronary artery disease and because of this preoccupation with adult cardiac disease and its requirements (coronary care units, facilities for angiography, angioplasty and bypass surgery), RHD receives much less attention as it is a disease of poor children who, as future citizens of the nation, should really receive high priority.

At present, the early detection of RHD through the SHS and PHC and secondary prophylaxis utilizing the SHS, PHC and GP remains the best available option. Should a safe vaccine become available, it would make a big difference to the control of the disease. The Central and State Governments should, meanwhile, cooperate in a major technology transfer session.

References

17. Pilot study on the feasibility of utilising the existing school and health services in Delhi for the control of RF/RHD, ICMR Final Report 1990
Cardiology at the Crossroads: Challenges for India and Lessons from the West

Bernard Lown
Professor Emeritus, Harvard School of Public Health, Boston, USA

Cardiology is now at a critical crossroad globally. We are living in an age of unprecedented medical progress. The innovations in cardiology, at times bordering on the miraculous, are compelled by inexorable advances in scientific knowledge. The present trajectory, though heady, is not sustainable and furthermore threatens to denature the moral core of our professionalism. Three developments have brought the issue into prominence. First is the emerging global pandemic of cardiovascular disease that will impact most decisively on poor developing countries. Second is the burgeoning cost of health care in rich countries that forces rationing of medical care along class lines. Third is the growing public discontent with, and alienation from, a technology-centered medical profession. These issues are interrelated and demand critical analysis. As is true of crises wrought by human agency, they challenge new thinking and offer opportunities for reaching a higher plateau of human service and development.

The CVD Pandemic in Developing Countries

While unable to shake the disease of poverty, a mounting epidemic of cardiovascular disease (CVD) is now sweeping the urban populations of the developing world. For the first time chronic degenerative ailments, generally associated with affluent societies, constitute a major cause of death in impoverished countries of the South. In 1990, two-thirds of the 14 million cardiovascular fatalities worldwide occurred in developing countries.1–3 These numbers are likely to increase as more than half the population is under 15 years of age. Furthermore in the developing world, CVD is emerging at an earlier age. In 1990 the proportion of CVD deaths occurring below the age of 70 years was 26.5% in rich countries as compared to 46.7% in poor countries.1 While the medical and socioeconomic consequences may prove ruinous, astonishingly the CVD epidemic in the South has received scant notice among physicians and public health professionals.4

Reasons for the increase in CVD are not mysterious. One important factor is the rising life expectancy. Other factors relate to rapid and chaotic urbanization with accompanying lifestyle changes and to the powerful economic and cultural influences of globalization.5 The shift in agricultural production from small farmer to large corporation, distribution from shopkeeper to supermarket, consumption from fresh to processed foods, promote drastic changes in nutrition. Junk food replaces dietary fiber and the complex carbohydrates of fruits and vegetables. Consumption of fat and salt increase and that of micronutrients diminish. Calorie intake multiplies while physical activity lessens. The mismatch between energy intake and energy output manifests in a pandemic of obesity.6 Crowding, mass unemployment and wanton violence engender social and psychological stresses which are additional risk factors for CVD and diabetes. When to this witch’s brew is added the rising consumption of tobacco, the outcome is as tragic as it is preordained.

The mounting scourge of cigarette smoking deserves a further comment. During the 1990s, the retreat of cigarette companies had become a near route in some industrialized nations. To make up for lost revenue, the tobacco companies forged a long-range global strategy to maintain sales roughly constant, where they were under siege, while investing mammoth resources to increase market share in the Third World. In the past decade tobacco consumption in the United States dropped 17 per cent while exports have skyrocketed 259 per cent.7 Tobacco promotion is pursued aggressively in less developed countries, with advertising budgets frequently surpassing national funds appropriated for leading diseases. Among the primary targets are women and children. These vulnerable groups are ill equipped to cope with the slick marketing techniques and the dirty tricks perfected by the tobacco industry.

Most developing countries have no advertising controls, lack adequate health warning requirements, and have a dearth of pressure groups campaigning for stricter tobacco controls. They have set no age limits, nor imposed restrictions on smoking in public places. Their populations are poorly educated on the health hazards, nor is...
information being provided to the burgeoning numbers of teenagers who are most susceptible to advertising hype. The higher tar and nicotine content purveyed to the developing world makes their cigarettes far more addictive and therefore more lethal. When the spreading tobacco habit is coupled with the rapidly rising prevalence of obesity and high blood pressure, guaranteed is the firestorm spread of ischemic heart disease.

How will India respond to this challenge? Current developments suggest that it will follow stereotypically the pattern evident worldwide. The role models are the industrial nations, particularly the USA. The emulation is in part driven by the fact that most developing countries have weak or nonexistent public health infrastructures, by their embrace of medical residency training programs aimed to impart proficiency in interventional technologies, and by the high incomes offered to those servicing wealthy clienteles in superspecialized sectors. Corporate-sponsored medical emporia are now mushrooming in urban centers all over the developing world. Interventional cardiology is a lucrative business. To attract “customers” no costs are spared in acquiring cutting-edge equipment serviced by highly trained professionals. Highlighted in these centers is specialized tertiary care treatment for those with ischemic heart disease while preventive strategies are largely ignored. In addition to the exorbitant social cost of such medical practice, it short-changes the individual patient by promoting unnecessary procedures which exact inevitable and unjustified burdens of morbidity as well as death.

Momentary reflection indicates that half-way technologies applied to advanced stages of disease are counterproductive strategies for containing an ever-mounting epidemic. An important warning sign about the road not to travel is now being provided by the USA, the chief advocate of a technological approach to health. The American people are now grappling with a health care crisis without seeming exit.

**USA—A Health System in Crisis**

A glance at any American cardiological journal convinces one that a majority of communications relate to promoting high-tech solutions. One unexceptional example, that of percutaneous transluminal coronary angioplasty (PTCA), is illustrative of some of the underlying factors in the present health care crisis. In 1978, Gruntzig et al. launched the era of interventional cardiology with introduction of this revolutionary approach. In 1991, a mere thirteen years later, more than 300,000 PTCA’s were performed annually in the USA at an estimated cost of US$7 billion. In the ensuing eight years, the number of coronary artery angioplasties more than doubled and now exceeds 700,000 annually. This near-exponential dissemination of PTCA occurred before the safety and efficacy of the procedure had been established. Though balloon dilatation effectively widens the caliber of a narrowed vessel in up to 90% of cases, it presents problems as yet unsolved. Foremost is the fact that restenosis occurs within six months in 30–50 percent of patients. Furthermore, PTCA does not protect against plaque rupture, the major cause of mortality in ischemic heart disease, nor does it deal with minor stenosis which constitutes the nidus for abrupt closures and resulting myocardial infarction. In fact, such unexpected closures occur after 2–5 percent of successful angioplasties.

The response to these limitations has been further addition of technologies such as stenting. In some countries intracoronary stent placement is used in 60% of percutaneous recanalization procedures. While stents reduce the restenosis rate of angioplasty by 30 percent or more, this is at a cost of neointimal proliferation. As could be expected, novel technologies are now on the ready to respond to this yet newer complication. Various types of endoluminal beta- and gamma-radiation therapies are purported to lessen neointimal growth, but not without additional complications which indubitably will beget still newer and costlier technologies.

When first introduced it was assumed that PTCA would reduce the far more expensive coronary bypass operation. This proved wrong. PTCA, by virtue of high rates of restenosis, did not affect the anticipated large cost savings, nor was there a decrease in the number of bypass procedures. In fact, the two have continued to increase in parallel. Furthermore, the exponential growth of PTCA, irrespective of its limitation, is driven by the fact that cardiologists who decide on its indication are the very ones who perform the lucrative procedure. Such self-referral is invariably associated with overuse of diagnostic or therapeutic interventions. Fueling the run-away exponential rise in these procedures relates to the fact that cardiology subspeciality academic programs overtrain residents in interventional techniques. It is not unexpected that those proficient in financially rewarding procedures try to maximize their performance. The enormous enrichment that awaits medical specialists has skewed the distribution of doctors in the USA away from primary care, with 70 percent now providing specialty care.

The consequences of uncontrolled technology usage in the USA, driven by other than evidence-supported medical indications, when multiplied across disciplines has powered astronomic health cost escalation. Last year, health
expenditures exceeded one trillion dollars (USA). My home state of Massachusetts, with only 6.3 million inhabitants, spends $5900 per person per year, which is more than is budgeted by the Indian government for health care with a population of one billion.

One would anticipate that with such mammoth expenditures, every single American would be receiving first class health care resulting in the best outcomes anywhere in the world. This is not the case. Forty-four million Americans are bereft of any health insurance and many more millions have inadequate health protection. In terms of outcomes, USA ranks an embarrassing 37th among 191 countries according to the World Health Organization. The ranking is based on such indicators as life expectancy, child survival to age five, out-of-pocket health expenditures and on a number of other factors which define high quality of care. In fact, a technologically focussed approach neither provides universal nor high quality health care.

The point is that the richest country in the world can not afford these enormous expenditures which are projected to double to 2.1 trillion dollars by the year 2007—a whopping 16.6% of America’s gross domestic product. To stem the inflation of costs, the USA has promoted the marketization of health services under the aegis of investor-owned health maintenance organizations (HMO). The intent is to enforce financial discipline by subjecting health care to the efficiencies of industrialization. Ignored is the commonsense fact that human beings cannot be standardized; overlooked is the fact that health care is a customized service resisting commodification and therefore incompatible with the efficiencies of industrialized assembly line or other mass production technologies.

The market solution is now widely acknowledged to have failed. It has not contained costs, not promoted universal access, nor maintained the quality of care. These outcomes have not been unexpected. As in any business enterprise, a paramount objective is to meet the profit expectations of investors. To achieve this objective, HMOs have recruited the healthy and short-shrifted the sick, have markedly curtailed hospital stays, and have down-sized hospital staff especially by reducing the cadre of experienced nurses. At the same time, doctors have been inundated with a glut of paper work responding to draconian measures to enhance efficiency and profitability. Less money has been made available for patient care as a large percentage of insurance premiums have been diverted from health related programs to dividends for investors, to increased market share through costly promotion campaigns and for egregious executive salaries, commonly in excess of onemillion dollars annually. Limiting physician autonomy in patient management has undermined the morale of the doctor and reduced it to an all-time low. The lack of professional satisfaction has led to early burn-out among increasing numbers of doctors.

There is a growing appreciation that the present direction of health care in the USA is untenable. It is widely agreed that though the American gross national product is $8 trillion annually, the growth in the level of health expenditures in the long run is unaffordable. A curative approach based on high technological investment surely is not an appropriate direction for poor developing countries.

Preventive Cardiology

Far more attractive practically as well as fiscally is a preventive strategy. Epidemiological studies extending over half a century have unearthed a wealth of information as well as forged an effective strategy for containing the epidemic of ischemic heart disease. The initial impetus was provided by the surveillance of nearly an entire population in the small Massachusetts community of Framingham. As a result of the accumulated evidence, primary prevention is now a challenging possibility. The essential concept is straightforward—readily identifiable risk factors long antedate the emergence of CHD. Cardiovascular death strikes not as an unexpected bolt of lightning but as the culmination of a slowly evolving process marked by readily recognizable signposts.

Much of the burden of heart disease is propelled by four easily recognized and modifiable factors such as elevated cholesterol, high blood pressure, cigarette smoking and physical inactivity. Extensive population studies demonstrate a continuous association between plasma cholesterol levels and the risk of coronary artery disease. Multiple clinical trials have also established that treating hypertension reduces the toll of cardiovascular disorders. This is true as well for cessation of smoking and physical inactivity.

Availing themselves of these new insights, industrialized societies have effected a substantial reduction in cardiovascular mortality during the last half of the 20th century. In the USA, during the three decades from 1960 to 1990, the CHD incidence receded about 1% annually with a concomitant decline in CHD mortality. In large measure the decline relates to modification of CHD risk factors. While improvement in treatment has contributed to this trend, the onset of the decline antedates the high volume of high-tech medical interventions.

That a concerted national effort can effect a striking change in CVD mortality has been dramatically
demonstrated in Finland. Heart disease mortality there, the highest in the world, exhibited the steepest decline anywhere recorded.\textsuperscript{27,28} Within a single generation the risk factor profile of the Finnish people has been changed. Dietary alteration involving lower fat consumption has decreased mean levels of serum cholesterol, at the same time, smoking has diminished among men while control of hypertension has been improved. The exemplary health dividend has been a 50% reduction in cardiovascular mortality in both middle-aged men and women.\textsuperscript{29}

Primary prevention is indispensable to reduce the CVD burden. Although considering the big canvas, more promising is a population-based strategy to prevent the emergence of risk factors rather than their amelioration in individual patients.\textsuperscript{30} Primordial prevention was first suggested by Strasser in 1980, to focus on preventing the emergence of major risk factors as a prominent component of public health strategy for containing the toll of CVD.\textsuperscript{31} As elegantly argued by Geoffrey Rose, a small shift in the population mean of a particular risk factor is associated with a large change in the prevalence of high values.\textsuperscript{32} For example, if the mean of cholesterol distribution in a population is reduced by 6\%-7\%, the prevalence of hypercholesterolemia (defined by the top decile) will be halved. Likewise a reduction in the population mean of systolic blood pressure of 8 mm will reduce the prevalence of hypertension by 50%. Rose cogently reasoned that a population-based approach is likely to be far larger, less costly, much safer and better sustained than the current practice of dealing with the individual patient. Primordial and primary prevention are complementary. Their essence is the promotion of healthier lifestyles for entire populations.

For cardiologists the principal responsibility is the optimal management of individual patients entrusted to their care. But I would maintain that our professional commitment to health mandates also a leadership role in community education on the optimal thoroughfare to healthy living. These are interrelated mutually reinforcing strategies.

Even in managing the individual patient, a higher premium has to be given to secondary prevention. Here the cardiologist confronts a pharmacological revolution that has drastically improved the prognosis of heart disease and has reduced the need for costly hospital-based interventions. Novel therapies are being introduced for each of the multifactorial elements contributing to the disease, such as beta-blockers, aspirin, antihypertensives, angiotensin-converting enzyme inhibitors, antidiabetic agents, etc. Introduction of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) has been among the most effective. It is clear that treating hypercholesterolemic patients with statins reduces the incidence of fatal and nonfatal myocardial infarction by 30\%-35\%, as well as lowering the incidence of strokes and the need for bypass surgical procedures.\textsuperscript{33-36}

To cite further examples, we at the Lown Cardiovascular Group, have over many years focused on secondary prevention and shown that it is possible to reduce by a formidable 80\% the need for coronary bypass, angioplasty, and stenting in patients with multivessel coronary artery disease. Long range outcomes in survival, incidence of myocardial infarction, as well as the quality of life have been of an order achieved with far more costly interventions.\textsuperscript{37-39} Whether focusing on the individual patient or on the larger community, the objective is a changed lifestyle. Central to its achievement is an informed public. Health education, therefore, can no longer be viewed as a discretionary component of care, rather, it needs to be considered essential to a comprehensive approach to CVD.\textsuperscript{39} In this respect a basis for hope is the ongoing digital information revolution, a social transformation of true epic proportions. In public imagination the information age is embodied in the Internet promising new vistas for democracy, education, and personal enrichment. Indeed, nothing in prior human history has provided as much potential for making readily available more information for more people at lower cost. In the USA the most popular are health websites. The existing 100 000 such sites are visited by 30 million Americans.

**New Directions and Novel Approaches**

Since the North has lived with the cardiovascular epidemic for half a century, the broad contours of this experience should prove instructive as the developing world confronts its own epidemic of CVD. Exploiting the new possibilities of the digital age is the unique, dynamic international forum, ProCOR, (a joint undertaking of the Lown Cardiovascular Research Foundation and SateLife,\textsuperscript{40} a leading provider of health information and communication services to health workers in developing countries), an ongoing, e-mail and web-based (www.ProCOR.org) electronic conference intent on fostering a global dialogue. This is to be a dialogue of equals where members of diverse constituencies from the medical profession, from among health care providers, from among those responsible for shaping and implementing health policy, and from community groups involved with health care, share know-how, timely information, experience, ideas, and proposals. Among key goals is to stimulate research in areas where there exists but a paucity
of reliable epidemiological data about incidence and trends in CHD risk factor prevalence. A further objective is to arouse the awareness of the cardiovascular community in the industrialized world, far too long blinded to the plight of the majority of humankind. Similarly to respond to the specific problems in particular countries, regional and national AmiCOR groups, (friends of ProCOR) have been promoted. In this global enterprise AmiCOR-india (registered domain name is http://www.amicorindia.org) is of special significance. This is supported by experts from Cardiology, Internal Medicine, Public Health and all other walks of life.

To launch an effective preventive strategy will mandate training a cadre of cardiovascular professionals who are sensitized to the issues and possess the appropriate public health tools. Discarding its past support to conventional cardiology training, the Lown Cardiovascular Group in collaboration with the Brigham and Women’s Hospital and the Harvard School of Public Health has initiated a new program for the exclusive training of cardiologists from the developing world. This encompasses a novel curriculum that will foster competence in both an holistic as well as a resource-conserving approach to patient management. Competence will be promoted in a number of disciplines related to identification of cardiovascular risk factors as well as community-based cardiovascular prevention programs. In addition to classical cardiovascular subjects, the curriculum will hone proficiency in an array of subjects; among these epidemiology, nutrition, biostatistics, cost-effectiveness analyses, informatics, medical technology assessment, socioeconomic determinants of health, and such unique areas as utilization of mass communication to effect behavioral changes as well as reshape cultural norms relating to health. Trainees will be encouraged to carry out research relevant to the particular needs in their countries. The program is to begin this year.

A growing understanding in the rich countries of the North is that without good health there cannot be economic development, a prerequisite for a stable world order. An important expression of that understanding is the CVD Research Initiative for the Developing Countries. Launched in 1998 through a partnership of Global Forum for Health Research (GFHR) and the World Health Organization, it is a key risk factor in high blood pressure. While hypertension is a growing problem in the developing world, it is a key risk factor in India where one out of three deaths is due to heart disease.

Conclusions
Preventive cardiology has now come of age. It is no longer tolerable to our conscience as health professionals to ignore this effective strategy. The stakes are not to be measured merely in unaffordable economic costs, but in preventing untold misery and denying people a longer life span. The cardiology profession is challenged to lead this important campaign for promoting good health for all segments of society. We have just crossed the threshold of a new century. The start of a new millennium is reason enough for an innovative and determined resolve.

Acknowledgments
The author acknowledges gratefully the constructive comments of RS Vasan, MD, DM, Framingham Heart Study (USA), and A Chockalingam, PhD, Ottawa (Canada).

References
2. Dodu SRA. Emergence of cardiovascular disease in developing countries. Cardiology 1988; 75: 56–64
25. Feinleib M. The downward trend and nature of the decrease in coronary artery disease mortality rate. Am J Cardiol 1984; 54: 2C–6C
36. Hebert PR, Gaziano JM, Chan KS, Hennetens CH. Cholesterol lowering with statin drugs, risk of stroke and total mortality. JAMA 1997; 278: 313–321
Absence of Association Between Serum Homocysteine Levels and Coronary Artery Disease in South Indian Males

R Deepa, K Velmurugan, G Saravanan, K Karkuzhali, V Dwarakanath, V Mohan
Madras Diabetes Research Foundation, Gopalapuram, Chennai
Department of Cardiothoracic Surgery, Government General Hospital, Chennai

Background: Asian Indians are reported to have a very high prevalence of premature coronary artery disease. However, traditional risk factors do not explain this excess of coronary artery disease. Elevated levels of homocysteine are associated with coronary artery disease among Europeans. This study looked at the association of serum homocysteine levels with coronary artery disease in South Indians.

Methods and Results: Four groups of patients were studied: Group 1 consisted of healthy nondiabetic subjects without coronary artery disease (n=18); Group 2 consisted of nondiabetic subjects with coronary artery disease (n=21); Group 3 consisted of type 2 diabetic patients without coronary artery disease (n=18) and Group 4 consisted of type 2 diabetic patients with coronary artery disease (n=20). The mean homocysteine value was 12.4±3.4 µmol/L in Group 1; 12.6±4.6 µmol/L in Group 2; 10.1±4.4 µmol/L in Group 3; and 10.4±3.9 µmol/L in Group 4. There was no significant difference in the homocysteine levels between the groups studied. The prevalence of hyperhomocysteinemia, defined as a level of 17.1 µmol/L (the 95th percentile for serum homocysteine in the control group) was not significantly different among the groups.

Conclusions: Elevated serum homocysteine levels are not associated with coronary artery disease in South Indian male subjects with or without diabetes. However, the results must be interpreted with caution because of the small numbers studied. (Indian Heart J 2001; 53: 44-47)

Key words: Hyperhomocysteinemia, Coronary disease, Risk factors

Hyperhomocysteine, a thiol containing amino acid generated during the metabolism of methionine, occurs in almost all human tissues. Elevated levels of homocysteine are associated with vascular disease and hyperhomocysteinemia is thus considered to be an independent risk factor for coronary artery disease (CAD). Factors which influence the levels of homocysteine include age, genetics, and nutrition. Since genetic background and nutritional intake vary in different populations, studies on homocysteine levels in different ethnic groups are necessary.

Asian Indians have very high prevalence rates of premature CAD occurring below the age of 50 years. Conventional risk factors do not fully explain the excess of CAD among Indians, hence the need for studying newer cardiovascular risk factors. The increased susceptibility to CAD in this ethnic group suggests that genetic factors may play a role. As homocysteine levels are genetically determined, we undertook a study of homocysteine levels in South Indian diabetic and nondiabetic subjects with and without CAD in Tamil Nadu state (South-East India).

Methods

Study Groups: We restricted the study to males as we could not obtain a sufficient number of well-characterized female subjects. The following groups of subjects were studied:

Group 1 consisted of 18 healthy nondiabetic control subjects, selected from an ongoing population-based study by the Chennai Urban Population Study (CUPS), Chennai. The inclusion criteria were: normal glucose tolerance test, absence of angina, myocardial infarction or any history of vascular disease and a normal resting 12-lead electrocardiogram (ECG).

Group 2 consisted of nondiabetic patients with CAD. Twenty-one male patients were selected from the department of Cardiothoracic Surgery, Government General Hospital, Chennai. CAD was diagnosed on the basis...
of coronary angiography and all the subjects had severe (>70%) stenosis of two or more coronary arteries.

Groups 3 and 4 were type 2 diabetic patients selected from the MV Diabetes Specialities Centre, a tertiary diabetes care center at Chennai. The diagnosis of diabetes was based on past medical history, drug treatment for diabetes (insulin or oral hypoglycemic agents) and/or criteria laid down by the WHO Consultation Report,16 i.e. fasting plasma glucose ≥ 126 mg/dl and/or 2 hour plasma glucose ≥ 200 mg/dl.

Group 3 consisted of 18 type 2 diabetic patients without CAD. All patients in this group denied any history of angina or myocardial infarction, had no history of any vascular disease and had normal resting 12-lead ECGs.

Group 4 consisted of 20 type 2 diabetic patients with CAD, which was diagnosed angiographically using criteria similar to those for Group 2.

The study protocol was approved by the ethical committee of our center and informed consent was obtained from all the study subjects. Clinical examination included measurement of height, weight, calculation of body mass index, blood pressure measurement and cardiovascular examination.

Biochemical Methods: A fasting blood sample was taken from all the study subjects for the estimation of plasma glucose, serum lipids and homocysteine. Homocysteine was assayed by enzyme-linked immunoassay (ELISA) using an Axis Biochemicals kit (Bio Rad, CA, USA). Briefly, protein-bound homocysteine in the serum sample is reduced to free homocysteine and converted enzymatically to S-adenosyl homocysteine (SAH) before the immunoassay. This is followed by a solid-phase enzyme immunoassay based on competition between SAH in the sample and immobilized SAH bound to the wall of the microtiter plate for binding sites on a monoclonal anti-SAH antibody. After removal of the unbound anti-SA antibody, a secondary rabbit anti-mouse antibody labeled with the enzyme horseradish peroxidase is added. The peroxidase activity is measured spectrophotometrically after addition of the substrate. The absorbance is inversely related to the concentration of total homocysteine in the sample. A calibration curve is constructed using a standard (2.0 – 50.0 µmol/L) provided with the kit. The inter- and intra-assay coefficient of variation of the homocysteine assay was 8.3% and 9.8%, respectively. Total serum cholesterol, serum triglyceride and HDL cholesterol were assayed with a commercial kit (Boehringer Mannheim, Germany) using the Hitachi 912 Autoanalyzer (Boehringer Mannheim, Germany). LDL was calculated using the Friedewald equation.17

Hypertension was diagnosed based on a history of drug treatment or if the blood pressure was greater than 140/90 mmHg.18

Statistical analysis: One-way ANOVA was used to compare the mean of the continuous variables among the study groups. Chi-square test or Fisher’s exact "t" test were used as appropriate to compare the proportions. All analyses were performed with the SPSS statistical software package (Version 4.0.1. SPSS, Chicago) and p values <0.05 were considered significant.

Results

Table 1 shows the clinical and biochemical features of the study population. Both the diabetic and nondiabetic patients with CAD had a higher prevalence of hypertension and smoking. Both the diabetic groups had higher serum cholesterol and serum triglyceride levels compared to the respective nondiabetic groups.

There was no difference in the mean homocysteine levels in the subjects, with or without CAD, either in the diabetic or in the nondiabetic subjects. The 95th percentile for serum homocysteine in the control group was 17.1 µmol/L. Using this as the definition, the prevalence of hyperhomocysteinemia was not significantly different among the groups.

There was a wide scatter of the values in the distribution of homocysteine in the study groups as seen in Fig. 1.
Recent reports on homocysteine suggest that it is an independent predictor of vascular disease, including stroke and CAD. A recent study has demonstrated the association of plasma homocysteine with increased CAD among immigrant Indians in the UK. However, a study from Singapore showed no increase in homocysteine levels in Indians compared to the Malays and Chinese. There are very few studies on homocysteine levels in native Indians. The present study shows a lack of association of homocysteine with CAD in native Indians. Similar results were obtained in a study from Kerala in South-West India. However, these results must be interpreted with caution in view of the limitations of the study mentioned below.

Recent studies on homocysteine in Indian diabetic patients have revealed an association of body weight with plasma homocysteine levels. The study by Munshi et al. showed elevated homocysteine levels in diabetic subjects compared to age-matched controls. Hoffman et al. reported that hyperhomocysteinemia is more common in type 1 diabetic patients with nephropathy. It was recently demonstrated that insulin may play a role in homocysteine metabolism and obese type 2 diabetics tend to have higher levels of homocysteine due to hyperinsulinemia. Our data show that there was no significant increase of homocysteine levels in diabetes per se or in diabetic patients with CAD. This could be attributed to the fact that the body-mass index was similar among the study groups.

One of the reasons for the discrepancy in results obtained from studies carried out on Europeans and Indians may be due to the differences in dietary habits. In India, many people are vegetarians and there is a higher intake of green leafy vegetables that are rich in folate which is an essential co-factor in the metabolism of homocysteine. It is well known that hyperhomocysteinemia can be corrected by increasing folic acid and pyridoxine intake. Unfortunately, we did not carry out any measurements of pyridoxine or B12 in our study.

A recent study from the Hammersmith Hospital, UK has reported that supplementation of folic acid and vitamin B12 improves vascular endothelial function. This effect is probably mediated through reduction in plasma homocysteine concentrations. However, in contrast a report from Addenbrooke's Hospital, UK reported no significant change in arterial stiffness in acute hyperhomocysteinemia induced by an oral methionine load. Overall, the association of homocysteine with CAD is still unclear and the American Heart Association has not recommended testing for homocysteine as part of the screening for cardiovascular risk in population-based studies.

Conclusions: The present study suggests a lack of association between homocysteine and CAD in urban South Indian male diabetic and nondiabetic subjects. The results, however, must be interpreted with caution due to several limitations of this study. Firstly, the sample size was very small. Secondly, we did not adjust for other cardiovascular risk factors, again due to the small sample size. Moreover, while the groups with CAD were diagnosed based on coronary angiography, the diagnosis in patients without CAD was made on clinical grounds and resting ECG findings. One cannot exclude the possibility that had coronary angiography been performed, some of these individuals might have had CAD. This could not, however, be done because of logistic, ethical and socio-economic reasons. Finally, only a fasting homocysteine (basal) sample was estimated. If an oral methionine load was given, the results may well have been different. Prospective studies are clearly needed to study the role of homocysteine in the development of CAD in native Indians.

Acknowledgments

Mr AK Mathai, for statistical analysis and Mrs G Malarvizhi and Mrs Muthuvalli Nayaki for secretarial assistance.
References

Does Inhaled Nitric Oxide Improve Survival in Operated Congenital Disease with Severe Pulmonary Hypertension?

R Sharma, N Raizada, SK Choudhary, A Bhan, P Kumar, R Juneja, SS Kothari, A Saxena, P Venugopal
Cardiothoracic Center, All India Institute of Medical Sciences, New Delhi

Background: The present study aimed to assess the impact of inhaled nitric oxide on survival following correction of congenital heart defects with residual pulmonary arterial hypertension.

Methods and Results: Inhaled nitric oxide was utilized for the management of residual pulmonary hypertension in 24 children following surgical correction of their underlying heart defects. Their ages ranged from 15 days to 14 months (median 5 months). Pulmonary artery hypertension was diagnosed either by direct pulmonary artery pressure monitoring or by echocardiography. Inhaled nitric oxide was used electively in 22 patients when the ratio of the mean pulmonary arterial pressure and mean systemic arterial pressure exceeded 0.5. In the remaining 2 patients, nitric oxide was used only to manage a pulmonary hypertensive crisis. Inhaled nitric oxide was also used a second time in 2 patients who developed delayed pulmonary hypertensive crisis. Twenty-two patients showed an initial response to therapy and the pulmonary artery pressures dropped significantly. Of the patients on direct pulmonary artery pressure monitoring, a pulmonary artery to systemic artery pressure ratio below 0.3 on prolonged therapy was associated with a survival ratio of 4/6 (including 1 neurological death and one re-operation); that between 0.3 and 0.5 with a survival ratio of 3/4. Three out of four patients with sustained echocardiographic and clinical response also survived and were discharged from the hospital. All the patients who showed a lack of response to (n=2), tolerance to (n=1), or dependence on (n=6) the use of inhaled nitric oxide died. In addition, all 5 patients who had a pulmonary hypertensive crisis died, 3 in spite of successful resuscitation with nitric oxide. Thus, excluding one neurological death and one re-operation, only 9 (41%) out of 22 patients survived.

Conclusions: Though inhaled nitric oxide is effective in lowering pulmonary pressure, it does not appear to improve the survival rate following repair of congenital heart disease in those with associated severe pulmonary hypertension. A randomized trial between the use and non-use of inhaled nitric oxide is warranted to determine its exact role in influencing survival in patients with residual pulmonary hypertension following surgical repair.

(Indian Heart J 2001; 53: 48–55)

Key Words: Pulmonary hypertension, Nitric oxide, Congenital heart defects

Several reports of the beneficial effect of inhaled nitric oxide (INO) in lowering pulmonary artery pressure (PAP) following repair of congenital heart disease are available.1-3 Yet, it is not clear whether this translates into survival benefit. Most centres with experience of INO belong to the developed world where surgery for congenital heart disease associated with significant pulmonary arterial hypertension (PAH) is undertaken in the neonate or very young infant. At this age, an accurate surgical repair is generally sufficient to prevent life-threatening PAH in the postoperative period.

The situation in the developing world is different in that late presentation of congenital heart disease is not uncommon and postoperative PAH is the principal determinant of the final outcome.4 The present report describes our early experience with INO in the management of postoperative PAH.

Methods

Patient population: Twenty-four children operated upon for various congenital heart diseases with severe PAH during
May–October 1999, who were put on iNO in the immediate postoperative period, form the basis of this report. Morphological diagnoses included ventricular septal defect (VSD, n = 7), obstructed total anomalous pulmonary venous drainage (TAPVC, n = 4), atrioventricular septal defects (AVSD, n = 2), single ventricle (n = 1), transposition of the great arteries (TGA, n = 8), and double outlet of the right ventricle (DORV, n = 2). The ages ranged from 15 days to 14 months (median 5 months). Patient details are summarized in Table 1.

**Preoperative evaluation:** A diagnosis was reached by two-dimensional echocardiography. Operability was assessed based on the clinical features, i.e., age, presence of congestive heart failure, cardiomegaly, features of left ventricular volume overload, presence of a mitral or tricuspid flow rumble, plethoric lung fields on plain chest X-ray and arterial oxygen saturation in room air and with oxygen. In borderline cases, cardiac catheterization was carried out to calculate the pulmonary vascular resistance in room air and on 100% oxygen. Systemic and pulmonary flows were calculated by the Fick technique and oxygen consumption was calculated from the assumed oxygen consumption formula.7

**Surgical management:** Standard techniques of cardiopulmonary bypass with deep or moderate hypothermia were utilized. Intracardiac repair was accomplished during a period of aortic cross-clamping with cardiac asystole achieved by 1 or more doses of anterograde cardioplegia delivered to the aortic root. Patients were routinely weaned away from cardiopulmonary bypass on a low dose of dopamine. Most patients had monitoring lines inserted for the measurement of pulmonary arterial (n = 14) systemic arterial oxygen saturation.

### Table 1. Preoperative characteristics

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Morphological diagnosis</th>
<th>Additional information</th>
<th>Age</th>
<th>Systemic arterial oxygen saturation</th>
<th>CTR</th>
<th>QP/QS</th>
<th>PAP/SAP</th>
<th>PVRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Room air 100% oxygen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>VSD</td>
<td>-</td>
<td>8 months</td>
<td>100% -</td>
<td>0.6</td>
<td>1.8/1</td>
<td>0.9</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>VSD</td>
<td>Absent LPA</td>
<td>8 months</td>
<td>100% -</td>
<td>0.6</td>
<td>&gt;2/1</td>
<td>0.7</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>VSD</td>
<td>-</td>
<td>12 months</td>
<td>100% -</td>
<td>0.5</td>
<td>1.6/1</td>
<td>1.0</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>VSD</td>
<td>Down syndrome</td>
<td>9 months</td>
<td>100% -</td>
<td>0.5</td>
<td>1.2/1</td>
<td>1.0</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>VSD</td>
<td>Small RV</td>
<td>6 months</td>
<td>100% -</td>
<td>0.6</td>
<td>&gt;2/1</td>
<td>1.0</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>VSD</td>
<td>Small RV</td>
<td>4 months</td>
<td>100% -</td>
<td>0.7</td>
<td>1.4/1</td>
<td>0.9</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>VSD</td>
<td>-</td>
<td>5 months</td>
<td>100% -</td>
<td>0.5</td>
<td>1.5/1</td>
<td>0.8</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>TAPVC</td>
<td>Infra-diaphragmatic</td>
<td>1 month</td>
<td>92% -</td>
<td>0.5</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>9</td>
<td>TAPVC</td>
<td>Supracardiac</td>
<td>53 days</td>
<td>91% -</td>
<td>0.5</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>10</td>
<td>TAPVC</td>
<td>Infra-diaphragmatic, meconium aspiration</td>
<td>15 days</td>
<td>50% - 60%-66%</td>
<td>0.5</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>11</td>
<td>TAPVC</td>
<td>Infra-diaphragmatic</td>
<td>3 months</td>
<td>40%-60% 60%-80%</td>
<td>0.5</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>12</td>
<td>CAVC</td>
<td>Down syndrome</td>
<td>8 months</td>
<td>80% 88%</td>
<td>0.5</td>
<td>2/1</td>
<td>1.0</td>
<td>11</td>
</tr>
<tr>
<td>13</td>
<td>CAVC</td>
<td>Down syndrome</td>
<td>5 months</td>
<td>82% 92%</td>
<td>0.6</td>
<td>&gt;2/1</td>
<td>1.0</td>
<td>10</td>
</tr>
<tr>
<td>14</td>
<td>SV</td>
<td>BAS+PA band at 2 months</td>
<td>6 months</td>
<td>60% 70%</td>
<td>0.5</td>
<td>0.8/1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>15</td>
<td>TGA</td>
<td>VSD</td>
<td>7 months</td>
<td>60% 75%</td>
<td>0.5</td>
<td>0.5/1</td>
<td>1.0</td>
<td>8</td>
</tr>
<tr>
<td>16</td>
<td>TGA</td>
<td>VSD</td>
<td>3 months</td>
<td>57% 65%</td>
<td>0.7</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>17</td>
<td>DORV</td>
<td>VSD</td>
<td>2 months</td>
<td>80% 92%</td>
<td>0.7</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>18</td>
<td>TGA</td>
<td>VSD</td>
<td>2 months</td>
<td>90% 92%</td>
<td>0.7</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>19</td>
<td>TGA</td>
<td>VSD</td>
<td>8 months</td>
<td>75% 82%</td>
<td>0.7</td>
<td>&gt;2.5/1</td>
<td>0.7</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>TGA</td>
<td>VSD</td>
<td>4 months</td>
<td>88% 95%</td>
<td>0.5</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>21</td>
<td>TGA</td>
<td>VSD</td>
<td>5 months</td>
<td>60% 70%</td>
<td>0.6</td>
<td>&gt;2/1</td>
<td>1/1</td>
<td>13</td>
</tr>
<tr>
<td>22</td>
<td>TGA</td>
<td>VSD</td>
<td>14 months</td>
<td>90% 94%</td>
<td>0.6</td>
<td>&gt;2/1</td>
<td>1/1</td>
<td>10</td>
</tr>
<tr>
<td>23</td>
<td>DORV</td>
<td>VSD</td>
<td>12 months</td>
<td>85% 92%</td>
<td>0.6</td>
<td>&gt;2/1</td>
<td>1/1</td>
<td>8</td>
</tr>
<tr>
<td>24</td>
<td>TGA</td>
<td>IVS, Post Senning</td>
<td>8 months</td>
<td>90% 92%</td>
<td>0.5</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

*Not catheterized

CTR: cardiopulmonary ratio; QP/QS: pulmonary to systemic blood flow ratio; PAP/SAP: ratio of mean pressure in pulmonary artery and systemic artery; PVRI: pulmonary vascular resistance (indexed); VSD: ventricular septal defect; LPA: left pulmonary artery; TAPVC: total anomalous pulmonary venous connection; CAVC: complete atrioventricular canal; BAS: balloon atrial septostomy; TGA: transposition of the great arteries; IVS: intact ventricular septum; DORV: double outlet right ventricle; RV: right ventricle; SV: single ventricle
and left atrial (n=16) pressures to assist in postoperative management. After arrival in the intensive care unit (ICU) a check echocardiogram was carried out in all patients to exclude significant residual defects.

**Diagnosis of postoperative PAH:** Fourteen of the 24 patients had direct PAP monitoring via a 20-gauge catheter inserted into the main pulmonary artery at the conclusion of surgery. Two had a pressure monitoring line in the right ventricular cavity inserted via the right atrial appendage and one patient's PAP was reflected in the internal jugular vein. The remaining 7 patients were diagnosed to have PAH in the post-repair period based on indirect evidence corroborated by Doppler echocardiography. Echocardiographic visualization of the dilated right heart chambers along with a Doppler velocity predictive of near-equalization of right ventricular and systemic pressures were taken to indicate the existence of severe PAH.

**Conventional management protocol for PAH:** Complete neuromuscular blockade using intermittent intravenous pancuronium and deep sedation by means of an infusion of fentanyl, for a period of at least 48 hours after surgery, were uniformly practised. In addition, an alkaline pH (>7.45) and hypocarbia (pCO₂ between 30 and 35 mmHg) in the arterial blood gas was ensured. An inspired FIO₂ of 1.0 was used in all patients with preoperative PAH in the early period following surgery and whenever the PAP showed a tendency to rise. In addition, a number of pulmonary vasodilators (nitroglycerine, isoprenaline, and prostaglandin E) were also used.

**Criteria for starting elective iNO therapy:** To use iNO, permission was taken from the hospital ethics committee. Informed consent was also taken from the parents of the children.

Any patient with a mean pulmonary artery to systemic artery pressure ratio (PAP/SAP) exceeding 0.5, which was sustained in spite of the above steps, was put on iNO therapy. In those without direct pulmonary artery pressure monitoring, indirect evidence that prompted echocardiographic interrogation for PAH included an episode of systemic hypotension with a high right atrial pressure (patients #17 and 20), unresolving pulmonary haemorrhage following repair (patient #18), features of a low cardiac output with resistant metabolic acidosis (patient #22), poor systemic perfusion with features of right heart failure (hepatomegaly, ascites) (patient #21) and hypoxemia and respiratory arrest in an extubated patient (patients #7 and 10). The temporal relationship between initiation of iNO therapy and the time after completion of surgical repair in each patient is mentioned in Table 1.

**iNO delivery system:** Medical grade nitric oxide (NO) in a concentration of 1000 parts per million (ppm) in nitrogen (Air Liquide®, France) was delivered via a Siemens Servo-300 ventilator modified for NO delivery and fitted with an electrochemical NO/NO₂ analyzer (Siemens Elema, AB, Sweden).

**iNO therapy protocol:** Therapy with iNO was begun at an initial dose of 10 ppm and increased in multiples of 10 ppm every 15 to 20 minutes in the absence of a significant response. Once a response was obtained, the dosage of iNO was decreased to the minimum at which this response persisted. In the absence of direct PAP monitoring, disappearance of an undesirable feature (e.g. metabolic acidosis or hepatomegaly), or improvement in systemic pressure, rise in peripheral skin temperature, improvement in diuresis, or increase in arterial oxygenation were sought and the minimum dose of iNO achieving that response was continued. Echocardiographic confirmation of the response was also looked for once a steady baseline had been achieved. No alterations in ventilator settings or drug infusions were made while the iNO therapy was being initiated and till the lowest possible steady maintenance dose was arrived at. Monitoring of toxicity was done by surveillance of the methemoglobin level and the percentage of inhaled nitrogen dioxide (NO₂). Methemoglobin levels, expressed as a percentage of the total hemoglobin, were measured every 12 hours during therapy. The electrochemical analyzer was used to monitor inhaled levels of NO. The protocol dictated reduction or cessation of therapy if the methemoglobin level exceeded 5%, or if the NO₂ level was 2.5 ppm or more.

**Weaning away from iNO:** An attempt to reduce iNO to the lowest effective dose was routinely made every 24 hours if hemodynamic stability and arterial oxygenation were maintained. If there was no adverse response to weaning at a rate of 2 to 5 ppm (especially if direct PAP was available), this was attempted every 6 hours. When down to a dose of 5 ppm, iNO was left on for at least 24 hours before further reduction was attempted. In general, complete cessation of iNO therapy and stability in this state for at least 24 hours were required before weaning away from mechanical ventilation. Some patients were kept on iNO (10 ppm) through an airtight hood with scavenging if they exhibited an elevation of PAP following extubation.

**Emergency use of iNO:** In the situation of a pulmonary hypertensive crisis with or without cardiorespiratory arrest,
iNO therapy was started at a dose of 80 ppm, if routine resuscitation measures failed to provide a prompt response. This was then reduced, if possible, in the steps described. A pulmonary hypertensive crisis was defined as an acute elevation of PAP such that PAP/SAP $> 1$ accompanied by systemic arterial desaturation with an impending or existential drop in systemic arterial pressure.

### Results

Following completion of surgery, iNO therapy was initiated at a mean interval of 20 hours (range 0 – 72 hours). The duration of therapy ranged from 1 to 10 days (mean 4.9 days). The response to iNO and final outcomes are summarized in Table 2.

Based on the initial response to iNO therapy, patients could be divided into 2 groups.

#### Table 2. Response to nitric oxide and final outcome

<table>
<thead>
<tr>
<th>Reference no. (Table 1)</th>
<th>Operation performed</th>
<th>iNO Therapy before extubation</th>
<th>Extubation</th>
<th>Secondary iNO</th>
<th>Lung infection</th>
<th>Final outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Indication</td>
<td>Interval between surgery and therapy (hours)</td>
<td>Resp.</td>
<td>Duration (days)</td>
<td>PAP/SAP</td>
</tr>
<tr>
<td>1</td>
<td>VSD closure</td>
<td>PA/PAP &gt;0.6</td>
<td>12</td>
<td>+ 4</td>
<td>0.3 - 0.5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>VSD closure</td>
<td>PA/PAP &gt;0.5</td>
<td>12</td>
<td>+ 3</td>
<td>0.3 - 0.6</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>VSD closure</td>
<td>PA/PAP &gt;0.5</td>
<td>24</td>
<td>+ 5</td>
<td>0.3</td>
<td>PAP/PAP &gt;0.6</td>
</tr>
<tr>
<td>4</td>
<td>VSD closure</td>
<td>Not required</td>
<td>24</td>
<td>+ 5</td>
<td>0.3</td>
<td>PAP/PAP &gt;0.8</td>
</tr>
<tr>
<td>5</td>
<td>VSD closure</td>
<td>PA/PAP &gt;0.8</td>
<td>48</td>
<td>+ 2</td>
<td>Never extubated to neurological complication</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>VSD closure</td>
<td>PA/PAP &gt;0.8</td>
<td>18</td>
<td>+ 5</td>
<td>PAP/PAP &gt;1.0</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>VSD closure</td>
<td>Not required</td>
<td>0</td>
<td>+ 4</td>
<td>0.4</td>
<td>PAP/PAP &gt;1.0</td>
</tr>
<tr>
<td>8</td>
<td>Repair</td>
<td>PA/PAP &gt;0.6</td>
<td>0</td>
<td>+ 3</td>
<td>0.2</td>
<td>PAP/PAP &gt;1.0</td>
</tr>
<tr>
<td>9</td>
<td>Repair</td>
<td>PA/PAP &gt;0.5</td>
<td>0</td>
<td>+ 4</td>
<td>0.2</td>
<td>PAP/PAP &gt;1.0</td>
</tr>
<tr>
<td>10</td>
<td>Repair</td>
<td>Not required</td>
<td>0</td>
<td>+ 4</td>
<td>0.2</td>
<td>PAP/PAP &gt;1.0</td>
</tr>
<tr>
<td>11</td>
<td>Repair</td>
<td>PA/PAP &gt;0.5</td>
<td>6</td>
<td>+ 5</td>
<td>Never extubated</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Repair</td>
<td>PA/PAP &gt;0.5</td>
<td>0</td>
<td>+ 7</td>
<td>Never extubated</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>Repair</td>
<td>PA/PAP &gt;0.5</td>
<td>0</td>
<td>+ 9</td>
<td>Never extubated</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>6</td>
<td>+ 1</td>
<td>#</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>24–26 mmHg</td>
<td>48</td>
<td>+ 5</td>
<td>0.2</td>
</tr>
<tr>
<td>16</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>24–26 mmHg</td>
<td>12</td>
<td>+ 7</td>
<td>0.5</td>
</tr>
<tr>
<td>17</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>24–26 mmHg</td>
<td>12</td>
<td>+ 2</td>
<td>0.5</td>
</tr>
<tr>
<td>18</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>24–26 mmHg</td>
<td>18</td>
<td>+ 5</td>
<td>0.5</td>
</tr>
<tr>
<td>19</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>24–26 mmHg</td>
<td>72</td>
<td>+ 2</td>
<td>0.5</td>
</tr>
<tr>
<td>20</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>24–26 mmHg</td>
<td>12</td>
<td>+ 2</td>
<td>0.5</td>
</tr>
<tr>
<td>21</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>24–26 mmHg</td>
<td>48</td>
<td>+ 9</td>
<td>0.5</td>
</tr>
<tr>
<td>22</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>24–26 mmHg</td>
<td>4</td>
<td>+ 10</td>
<td>0.5</td>
</tr>
<tr>
<td>23</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>24–26 mmHg</td>
<td>12</td>
<td>+ 8</td>
<td>0.5</td>
</tr>
<tr>
<td>24</td>
<td>Repair</td>
<td>SVC pressure</td>
<td>24–26 mmHg</td>
<td>12</td>
<td>+ 2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* No pulmonary artery catheter; ** NO dependence; = tolerance to NO; # reoperated with takedown of Bidirectional Glenn + banding of main pulmonary artery; Ñ : cardiopulmonary arrest but NO was not available; PAP/PAP : ratio of mean pressures in pulmonary artery and systemic artery; RV : right ventricle; PAH : pulmonary arterial hypertension
Responders: Twenty-two patients (#1–3, 5, 6, 8–24) showed an initial response to iNO. In those patients where direct PAP recording was available (n=15), mean PAP dropped from 47±18.0 mmHg to 23.5±15.1 mmHg (p<0.001). The fall in mean PAP ranged from 6 to 35 mmHg (mean 23.6±4.8 mmHg) and the PAP/SAP ratio stabilized to less than 0.5 in 10 patients. Seven patients without PAP monitoring showed echocardiographic evidence of a drop in PAP. In general there was improvement in the systemic arterial pressure, urine output and toetemperature in all 7 patients. One patient (#22) who had a persistent base deficit along with carbon dioxide retention in spite of supramaximal ventilation since arrival from the operating room, had a dramatic normalization of blood gases, so that ventilator settings could be rapidly revised. Another patient (#18) had pulmonary hemorrhage continuing into the second day following surgery. After echocardiogram detected a severe PAH based on a high-velocity pulmonary regurgitation jet filling the entire right ventricular cavity, iNO therapy was instituted expeditiously. Within an hour of starting 10 ppm iNO, the pulmonary hemorrhage became negligible. A check echocardiogram demonstrated significant reduction in the velocity of pulmonary regurgitation with improvement in right ventricular function.

Non-responders: Two patients (#4 and 7) showed no change in PAP irrespective of the iNO concentration. The first was a 9-month-old child with Down syndrome who had low PAP till the second day following extubation. Subsequently, he developed lung opacities with fever and his PAP rose from moderately to severely elevated levels without any response to iNO. He later succumbed to lung infection. Patient #7, who had been operated for a large VSD, developed systemic level PAP only following extubation which was completely unresponsive to repeated endotracheal intubation, 100% oxygen and iNO. He later succumbed to lung infection. Four patients (#6, 12, 13, 23) developed NO dependence and had a recurrence of acidosis and hypoxemia whenever either iNO or ventilatory weaning was attempted. They finally succumbed to overwhelming lung infection.

PAP/SAP 0.3–0.5: Four patients (#1, 2, 16, 24) were weaned away from iNO while their PAP/SAP ratio was between 0.3 and 0.5. This was because their PAP did not drop any further irrespective of the dosage of iNO. Moreover, they were hemodynamically stable at this PAP when iNO was finally discontinued for more than 24 hours. All of them were extubated successfully. However, patient #16 had a PAH crisis leading to respiratory arrest 4 days after extubation. He could be resuscitated only with iNO but this time could not be weaned away from iNO or the ventilator.

NO dependence: Four patients (#6, 12, 13, 23) developed NO dependence and had a recurrence of acidosis and hypoxemia whenever either iNO or ventilatory weaning was attempted. They finally succumbed to overwhelming lung infection.

NO tolerance: Patient #11, a 3-month-old child with obstructed infradiaphragmatic TAPVC demonstrated an initial response to iNO but later became non-responsive as his PAP gradually rose beyond the systemic level irrespective of the maximal dose of iNO. Before demise his PAP/SAP was 3/1.

Patients without PAP monitoring could not have an exact quantification and had to be grouped based on echocardiographic estimation of PAP reduction and clinical response.

Patients without PAP monitoring (#10, 17–22): Patient #10, who was on mechanical ventilation preoperatively for respiratory failure resulting from
meconium aspiration, had been doing well without the need for iNO in the entire postoperative period, but developed respiratory arrest 12 hours after extubation from which he could be resuscitated only with the use of iNO, once echocardiogram confirmed severe PAH. Patients #17, 18, 19 and 20, all of whom had TGA or DORV with large VSD, could be weaned away from iNO and from the ventilator. Patient #18 had a PAH crisis 7 days after successful weaning away from iNO and the ventilator and could only be resuscitated by restarting iNO. The other 3 recovered uneventfully. Patients #21 and 22 became iNO dependent and became hypoxicemic and acidotic on reducing iNO concentration. Both finally expired.

**PAH crisis:** Five instances (#7, 10, 15, 16, 18) of PAH crises were encountered (4 confirmed and #15 presumed). All presented with respiratory arrest either immediately or up to 15 days after extubation. Two (# 7 and 10) did not require iNO prior to extubation. The other three recovered well and were weaned away from both iNO and mechanical ventilation. Patient #7 showed no response to iNO while patients #10, 16 and 18 could be resuscitated only with use of iNO in the inhaled gas mixture. iNO was not available for #15. The 3 who were resuscitated successfully developed lung infection and could not be weaned away from iNO or the ventilator. None of the patients with a PAH crisis survived.

**Overall survival:** Two patients could not be completely evaluated with respect to the end-points of separation from iNO and the ventilator due to premature demise (#5, neurological problem) and re-operation (#14) for reversal of surgical repair. If these 2 were to be excluded, only 9 of 22 patients receiving iNO could be referred to as “successes”.

All nonsurvivors were either nonresponders, or those who developed iNO dependence, or had a PAH crisis following an initial satisfactory recovery.

**Discussion**

Most patients with reversible PAH of any etiology would show a reduction in PAP with iNO. This has been amply demonstrated in neonates with persistent fetal circulation, adult respiratory distress syndrome, and adults with operated valvular heart disease. In most of these conditions and others, however, it is unclear if the use of extrinsic NO can alter disease outcomes.

In the case of congenital heart disease per se, iNO has been introduced into the clinical arena in an era when the standard of health care in the developed world has made antenatal or immediate postnatal diagnosis of congenital heart disease a routine, thereby ensuring timely corrective surgery.

Because of the paucity of reports on the effect of the use of iNO in late presenters of congenital heart disease the role of iNO in this setting is as yet undefined.

Strategies for the management of the child with congenital heart disease with severe PAH who presents late are not clear. Operability denoted by conventional criteria such as a drop in pulmonary vascular resistance to acceptable levels on oxygen or iNO merely signifies a reactive pulmonary vascular bed. Patients, though declared operable by cardiac catheterization data, may have problems with persistent or episodic elevations of PAP. Final outcomes are then dependent on the subsidence of PAP or the capacity of the pulmonary ventricle to tolerate residual PAH. On clinical examination, 14 of the 24 children were thought to be within the borderline operable range and were therefore subjected to cardiac catheterization. As shown in Table 1, all 14 were deemed to be operable based on the catheterization data. As all patients showed a reduction in pulmonary vascular resistance to "operable" levels on oxygen, preoperative histological examination of the pulmonary vasculature was not thought to be necessary. Even with postoperative use of iNO, the safest and most potent pulmonary vasodilator known today, only 4 of these patients had a successful outcome.

Down syndrome (3 children in this series) is known for its rapid progression of pulmonary vascular disease when associated with a VSD or AVSD. Patient #4 (Down syndrome with a large VSD) had significant pulmonary vascular disease according to his preoperative data. He, however, had a benign postoperative course, till he developed pneumonia. Subsequent course (PAH unresponsive to iNO) demonstrates the lethal combination of PAH and pulmonary infection. The children with AVSD had only partial response to iNO and gradually worsened in the face of persistently elevated PAP. TGA with VSD is another lesion well known for early pulmonary vascular disease. Assessing pulmonary vascular resistance by the Fick principle in TGA is known to be fallacious as the arteriovenous oxygen differences are small and the assumed values for oxygen consumption are not reliable. What is more reliable with respect to pulmonary vascular resistance in patients of TGA with VSD is the clinical assessment and arterial oxygenation on room air and on 100% oxygen. Thus, given good mixing, the lower the arterial oxygenation the more the likelihood of an elevated pulmonary vascular resistance. Only 1 patient above 4 months of age with TGA and VSD survived. However, 2 patients less than 4 months of age also succumbed to PAH crises. Obstructed TAPVC is
also well known for accelerated pulmonary vascular changes.\textsuperscript{21} In our series, patient #12 who had an obstructed infradiaphragmatic TAPVC which was corrected at the age of 3 months, was certainly not a candidate for corrective surgery considering his postoperative behaviour in the presence of an unobstructed pulmonary venous chamber to left atrial anastomosis. Patient #9, in spite of presenting at almost 2 months of age with the same diagnosis, had a completely benign postoperative recovery.

Reactivity of the pulmonary vascular bed changed from the preoperative state following reparative surgery and was even seen to undergo a change in the postoperative phase of the same patient with time. Pulmonary capillary endothelial injury as a result of cardiopulmonary bypass is a well recognized cause of this state.\textsuperscript{24} A nother factor that seemed to play an important role in aggravating PAH was pulmonary infection. None of the delayed pulmonary hypertensive crises could progress to hospital discharge due to the development of secondary iNO dependence in patients who had previously been well controlled on iNO. The presence of pulmonary opacities with positive endotracheal cultures in these and other iNO-dependent patients in this series may point to a strong link between PAH and pulmonary infection. Exacerbation of subclinical infection or acquired infection secondary to prolonged endotracheal intubation could be one possibility. The other possibility is that of the pulmonary opacities being secondary to prolonged therapy with iNO. This cannot be dispelled entirely even though the NO concentration in the inhaled mixture never rose beyond 2 ppm and was usually below 1 ppm. It is disconcerting that other clinical series have also noted an increased incidence of pulmonary complications.\textsuperscript{4,5} It is important to note that these pulmonary opacities were seen in those patients who had received higher doses of iNO because of the relative non-responsiveness to lower initial doses.

The point at which iNO therapy should be initiated is unclear. In this study, a persistent PAP/SAP ratio of $\geq 0.5$ was taken as an indication for starting iNO. However, there were patients who were weaned away from iNO at this level of PAP/SAP if the other parameters did not suggest interference with normal cardiac performance. Perhaps iNO therapy should be initiated only if the PAP/SAP ratio is 0.5 and rising, and if the hemodynamics at that moment suggest interference with normal cardiac performance. The important question to answer is if any deleterious effect was caused by the suppression of endogenously derived relaxation factor by continuous administration of iNO\textsuperscript{25} and its possible role in the NO dependence that was observed in some patients.

In such a heterogeneous group of patients, in whom an elevated PAP is probably the only common denominator, it is not surprising that varied responses to iNO were observed. Thus there were patients who did not respond at all, there was one who responded initially and later became completely unresponsive, there were others who responded but became dependent on NO, and there were others who responded predictably throughout and could be weaned away and taken off mechanical ventilation. The 9 successful cases in this experience were indistinguishable from the 13 non-survivors based on preoperative characteristics like age, arterial oxygenation, pulmonary vascular resistance, etc. It is possible that preoperative histological grading of the lung vasculature may have provided some differentiation.\textsuperscript{26}

Two questions are unavoidable in a study of this nature: Are the successes (9 patients) attributable to iNO? Would patients who later became iNO dependent have had a different outcome if iNO had not been used at all? A randomized study with survival as an end-point is clearly indicated if we are to answer these questions.

Finally, based on this study, we would at best regard the outcome benefit with use of iNO as equivocal. Our initial impression (and expectation) from existing reports was one that forbade withholding iNO therapy from any patient with postoperative PAH. With the results of this initial experience we are now in a position to initiate a controlled trial with certain well-defined cross-over points between iNO and conventional therapy.

References

7. Fixler DE, Carrell T, Browne R, Willis K, Miller WW. Oxygen...
consumption in infants and children during cardiac catheterization under different sedation regimens. *Circulation* 1974; 50: 788–794
Original Article

Plasma Lipoprotein(a) Levels in Patients With Pulmonary Arterial Hypertension

Satyendra Tewari, Deepak Gupta, Sudeep Kumar, Naveen Garg, Madan M Godbole, Nakul Sinha
Department of Cardiology & Endocrinology
Sanjay Gandhi PGIMS, Lucknow

Background: Pulmonary artery hypertension is a common sequelae of a variety of cardiac and lung diseases. Pathogenesis of primary and secondary pulmonary artery hypertension is still debatable.

Methods and Results: We studied the serum lipoprotein(a) levels in patients with primary (n=27) and secondary (n=19) pulmonary artery hypertension (Eisenmenger syndrome). The results were compared with age and sex-matched controls (n=46). We also studied the frequency of high levels of lipoprotein(a) (>30 mg/dl) in pulmonary artery hypertension. Mean lipoprotein(a) levels were significantly higher in the pulmonary artery hypertension group compared to age- and sex-matched controls (31.60±15.49 mg/dl v. 14.66±14.7; p=0.0001). All patients were classified into two groups on the basis of their lipoprotein(a) levels (<30 mg/dl and >30 mg/dl). There was a higher frequency of lipoprotein(a) >30 mg/dl in patients of pulmonary artery hypertension v. controls (52% v. 24%; p= <0.001). Younger age, higher functional class, more severe congestive heart failure, shorter duration of symptoms, and more cases of hemoptysis were observed in the group with lipoprotein(a) >30 mg/dl.

Conclusions: High lipoprotein(a) may be a marker and be associated with a more adverse prognosis in severe pulmonary artery hypertension. Larger prospective studies are needed to establish lipoprotein(a) as a risk factor for the development of pulmonary artery hypertension. (Indian Heart J 2001; 53: 56–60)

Key Words: Lipoproteins, Pulmonary hypertension, Thrombosis

Lipoprotein(a) is a complex lipoprotein (Lp) macromolecule that contains apolipoprotein(a), which shares 80% to 90% homology with plasminogen. It acts as a competitive inhibitor of tissue type plasminogen activator and thereby helps in modulating the fibrinolytic system. Moreover Lp(a) is an important regulator of synthesis of plasminogen activator inhibitor (PAI-1) by endothelium. All these lead to a prothrombotic state. Pulmonary artery hypertension (PAH) is the common sequelae of a variety of cardiac and lung diseases. Exact pathogenesis of primary and secondary PAH is still debatable. Pulmonary thrombosis is a common feature of both primary and secondary PAH. Various defects of coagulation including von Willebrand factor, PAI-1 and defective fibrinolysis have been demonstrated in primary pulmonary artery hypertension (PPH). Lp(a) has also been implicated in thrombogenesis. The fact that PAH develops in only 6% of patients with secundum atrial septal defect (ASD) suggests that genetic predisposition may be necessary. Whether the Lp(a) is a novel risk factor for development of PAH has not been investigated. We studied the serum Lp(a) levels in patients with PPH and secondary PAH (Eisenmenger syndrome) and compared it with similar numbers of age- and sex-matched healthy volunteer controls.

Methods

Forty-six patients of severe PPH and PAH due to congenital left to right shunt were included in the study. PPH was diagnosed by exclusion of any form of secondary pulmonary hypertension (pulmonary embolism, chronic obstructive pulmonary disease, primary cardiac shunt, or connective tissue disease). Patients with secondary PAH included those with an intracardiac shunt lesion. The patients with PAH secondary to valvular heart disease, left ventricular dysfunction, collagen vascular disease and lung disease were excluded from the study. Other exclusion
criteria were renal failure, proteinuria, diabetes mellitus, acute inflammation, female patients taking oral contraceptive pills and alcoholism, as these are known to influence the Lp(a) level. Informed consent was obtained from each patient and the study protocol conformed to ethical guidelines. The initial assessment of patients included a complete history and physical examination, complete blood count, arterial blood gas analysis, biochemical screening, roentgenogram and urine analysis. Drug status of all patients was recorded, and they were then subjected to a 12-lead ECG, and a detailed echocardiography (two-dimensional, Doppler and color flow examination) performed on HP sonos5500 Ultrasound system (Hewlett Packard, Massachusetts; USA). Sera of all those in the study group (46 patients) and a similar number of age- and sex-matched control group (healthy volunteers) were taken for quantitative Lp(a) measurements.

Echocardiographic study: Estimated systolic pulmonary artery pressure (SPAP) was calculated by using a simplified Bernoulli’s equation [SPAP = 4 × (tricuspid regurgitation velocity)² + CVP]. A value of 10 mmHg was assumed for central venous pressure (CVP) in patients without any evidence of systemic venous congestion. Estimated systolic pulmonary arterial pressure >70 mmHg was taken as evidence of severe PAH. Two observers independently verified the echocardiographic measurements. Right ventricular systolic pressure (RVSP) equal to or more than 70 mmHg was taken as evidence of severe PAH. In patients with septal defects the pattern of flow across the shunt lesion was recorded, using colour flow imaging and pulsed wave Doppler examination. Contrast echocardiography using an agitated saline flush was done to evaluate shunt flow if colour flow imaging was unsatisfactory.

Blood sampling and assay: Fasting venous blood samples were collected. Blood was centrifuged for 10 minutes at 4°C and the serum stored at −70°C until analyzed (3–6 months). The Lp(a) level was measured with a commercially available ELISA kit (TintElize® Lp(a), Biopool International, Ventura, Ca, USA). The assay utilizes affinity-purified polyclonal antibodies raised against Lp(a).

Statistical analysis: All clinical, biochemical and echocardiographic data were recorded prospectively. We compared the Lp(a) level of patients with severe PAH with those of age- and sex-matched controls. Previous reports have suggested that >30 mg/dl is the threshold value linked to its pathological effects. Based on this value, we defined subjects with >30 mg/dl as those with high Lp(a) and examined its frequency in severe PAH. We also studied the association of high Lp(a) with demographic, clinical and echocardiographic variables. Continuous variables were reported as mean ± standard deviation. Differences in mean group values were analyzed by unpaired 2-tailed t-test for parametric data. The difference in categorical variables was compared with the use of the chi-square test. A value of p<0.05 was considered significant.

Results

Baseline characteristics of patients including the spectrum of symptoms, severity of right ventricular systolic pressure and mean Lp(a) level are shown in Table 1. The PPH group consisted of 27 patients whereas 19 patients had Eisenmenger syndrome (ES). The majority of ES patients had ASD (16 out of 19), while the rest had a ventricular septal defect (VSD). As shown in table 2, mean Lp(a) level is significantly higher in the PAH group compared to the age- and sex-matched controls (31.60±15.49 mg/dl vs. 14.66±14.7 mg/dl; p=0.0001). Serum Lp(a) levels by quintile is illustrated in Fig. 1. There was higher frequency...
of Lp(a) >30 mg/dl in patients of PAH than the control group (52% v. 24%; p<0.001). All patients were classified into two groups on the basis of their Lp(a) levels (Table 3). Younger age, higher functional class, more severe congestive heart failure, shorter duration of symptoms, and more hemoptysis were observed in the group with Lp(a) >30 mg/dl. R VSP was also significantly higher in this group (100.64±12.86 mmHg v. 86.42±13.9 mmHg; p<0.001).

Table 3. Clinical and echocardiographic profile in Lp(a) >30 mg/dl and Lp(a) <30 mg/dl group

<table>
<thead>
<tr>
<th>Lp(a) &gt;30 mg/dl (n=25)</th>
<th>Lp(a) &lt;30 mg/dl (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.84±5.26</td>
<td>28.62±7.6</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>12/13</td>
<td>6/15</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>5(20%)</td>
<td>9(42.8%)</td>
</tr>
<tr>
<td>Class III</td>
<td>4(16%)</td>
<td>8(38.1%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>16(64%)</td>
<td>3(14.4%)</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>15(60%)</td>
<td>4(19%)</td>
</tr>
<tr>
<td>Duration of symptoms (years)</td>
<td>1.84±0.5</td>
<td>2.29±0.6</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>9(36%)</td>
<td>1(4.76%)</td>
</tr>
<tr>
<td>R VSP (mmHg)</td>
<td>100.64±12.86</td>
<td>82.42±13.9</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPH</td>
<td>16(64%)</td>
<td>11(52.4%)</td>
</tr>
<tr>
<td>Eisenmenger syndrome</td>
<td>9(36%)</td>
<td>10(47.6%)</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; R VSP = right ventricular systolic pressure; PPH = primary pulmonary hypertension

Table 4. Demographic, clinical, echocardiographic profile and Lp(a) levels in PPH and Eisenmenger patients

<table>
<thead>
<tr>
<th></th>
<th>PPH (n=27)</th>
<th>ASD–Eisenmenger (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.85±7.7</td>
<td>25.56±5.9</td>
<td>0.44</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>62.96 %</td>
<td>62.5 %</td>
<td>0.83</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>1.9±0.5</td>
<td>2.19±0.7</td>
<td>0.08</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>5(18.5%)</td>
<td>8(50%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Class III</td>
<td>8(29.6%)</td>
<td>4(25%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Class IV</td>
<td>14(51.8%)</td>
<td>4(25%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>16(59%)</td>
<td>4(25%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>9(33.3%)</td>
<td>3(18.7%)</td>
<td>0.79</td>
</tr>
<tr>
<td>R VSP</td>
<td>101.0±13.9</td>
<td>94.12±13.44</td>
<td>0.04</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>33.14±15.6</td>
<td>33.15±13.9</td>
<td>0.49</td>
</tr>
<tr>
<td>Patients with Lp(a) &gt;30 mg/dl</td>
<td>59%</td>
<td>56%</td>
<td>0.81</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; R VSP = right ventricular systolic pressure; PPH = primary pulmonary hypertension

Table 5. Demographic, clinical and echocardiographic characteristics of PPH and ASD–Eisenmenger syndrome patients with Lp(a) levels >30 mg/dl

<table>
<thead>
<tr>
<th></th>
<th>PPH (n=16)</th>
<th>ASD–Eisenmenger (n=9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21.32±6.5</td>
<td>25.55±5.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/8</td>
<td>4/5</td>
<td>0.78</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>1.79±0.5</td>
<td>1.9±0.6</td>
<td>0.27</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>1</td>
<td>4</td>
<td>0.07</td>
</tr>
<tr>
<td>Class III</td>
<td>3</td>
<td>1</td>
<td>0.08</td>
</tr>
<tr>
<td>Class IV</td>
<td>12</td>
<td>4</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemoptysis no (%)</td>
<td>6(37.5%)</td>
<td>3(33.3%)</td>
<td>0.83</td>
</tr>
<tr>
<td>R VSP</td>
<td>101.0±14</td>
<td>100.0±10.7</td>
<td>0.42</td>
</tr>
<tr>
<td>CHF</td>
<td>10(62.5%)</td>
<td>5(55.5%)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; R VSP = right ventricular systolic pressure; PPH = primary pulmonary hypertension; CHF = congestive heart failure.

Discussion

The serum Lp(a) levels were significantly higher in the severe PAH group and were associated with a more advanced form of the disease. To the best of our knowledge, this study is the first Indian report to demonstrate a relationship between the Lp(a) level and PAH. Lp(a) was first described by Berg et al. as a lipoprotein-associated antigen with pre-beta electrophoretic mobility. Studies in Indian population have shown that Lp(a) levels are significantly higher among coronary artery disease (CAD) patients as compared to controls. Mohan et al. showed that Lp(a) was an independent risk factor for CAD in diabetic patients. In previously reported studies on Indian subjects, the mean values have ranged from 15.0 to 34.0 mg/dl in healthy controls and 20.0 to 41.0 mg/dl in patients with CAD. In a study of 1150 subjects involving...
seven ethnic groups, Lp(a) levels were almost twice as high in Asian Indians as compared to Caucasians, Malays, and Chinese residents of Singapore. In the CADI study on the immigrant Indian population Lp(a) levels >30 mg/dl were found in a higher proportion of Asian Indians as compared to Whites (25% vs. 17%).

Thrombosis in situ is considered as one of the pathogenic mechanisms in PPH. A thrombus may result from injury to the endothelium, abnormal fibrinolysis, enhanced procoagulant activity and/or platelet abnormalities. Both a retrospective analysis and a small nonrandomized prospective study suggest that anticoagulants prolonged the life span of patients with PPH. This also indirectly supports the role of thrombosis in the progression, if not the development, of PPH. There are in vitro and in vivo studies which support the theory that Lp(a) has a thrombogenic effect. In addition to PPH, thromboembolic phenomena have also been considered as the etiological basis of pulmonary hypertension in patients with left to right congenital shunts. Why a left to right shunt would produce miliary embolization in the lung has never been adequately addressed. In congenital heart disease it is probable that the increased pulmonary blood flow and development of high pressure over a period of time is associated with a high shear stress, resulting in one type of endothelial injury (VSD and plexogenic arteriopathy); whereas high pulmonary blood flow without increased pressure and shear stress produce a different endothelial response (ASD and thrombotic arteriopathy). The fact that pulmonary hypertension develops in only 6% of patients with ASD also suggests that a genetic predisposition may be important.

Recently serum Lp(a) has also been implicated as a risk factor for left atrial thrombus in patients with chronic atrial fibrillation. There are scanty reports of high Lp(a) levels in primary and secondary PAH patients. Increased plasma Lp(a) level in patients with chronic thromboembolic PAH has been reported by Ignastescu et al. Significantly high Lp(a) have been reported in both primary and secondary PAH by Santos et al. They compared the Lp(a) level of 32 caucasian PAH patients (both primary and secondary) with an equal number of healthy controls. Median Lp(a) level was significantly higher in PAH patients than in the control group (31.0 mg/dl (9.0–43.5) vs. 12.0 mg/dl (6.4–23.3) p=0.01). There was also a higher frequency of Lp(a) (>30 mg/dl) in patients with PAH than in the control group (90% and 50% respectively, p=0.006) in that study. In our study also, 52% of severe PAH patients showed high Lp(a) (>30 mg/dl) as compared to only 24% of the control group. Mean Lp(a) levels were significantly higher in PAH patients compared to the control group. Patients in the high Lp(a) (>30 mg/dl) group were younger, had more advanced heart failure with rapid progression of the disease, had more hemoptysis and higher pulmonary artery pressure as compared to the group with Lp(a) <30 mg/dl. Subgroup analysis of PPH and Eisenmenger groups showed no significant difference in demographic variables, severity of PAH (RVSP) and Lp(a) levels.

Our study suggests that a high Lp(a) level may be a novel risk factor for the development of both primary as well as secondary PAH due to congenital left to right shunt, particularly ASD. This newly described risk factor for development of PAH raises the issue of the importance of early therapeutic intervention in congenital heart disease with left to right shunt, particularly in patients with ASD with high Lp(a) level. In future there may be therapeutic methods to reduce Lp(a) levels which may prove to be useful in patients of PAH with less severe forms.

Study limitation: The study group consists of only a small number of patients. Other components of the fibrinolytic system were not evaluated. Therefore the relationship between Lp(a) and the fibrinolytic system remains unclear. Lp(a) of ASD-Eisenmenger patients was not compared with those of similar size of ASD with normal pulmonary artery pressure.

Conclusions: In patients with severe PAH the serum Lp(a) levels were significantly higher. High Lp(a) may be associated with a more adverse prognosis in severe PAH. Larger prospective studies are needed to establish Lp(a) as a risk factor for the development of PAH.

References
1. Eaton DL, Fless GM, Ohr WJ, Mclean JW, Xu QT, Miller CG, et al. Partial amino acid sequence of apolipoprotein(a) shows that it is homologous to plasminogen. Proc Natl Acad Sci USA 1987; 84: 3224–3228
23. Isser HS, Puri VK, Narain VS, Saran RK, Dwivedi SK, Singh S. Lipoprotein(a) and lipid profile in young patients with myocardial infarction and their first degree relatives (Abstr). Indian Heart J 1998; 50: 626
28. Jose JV, Selvakumar D, Selvakumar, Kangasababapathy, Serum lipoprotein(a) levels in ischemic heart disease. J Assoc Phys India 1997; 45: 766–768
38. Santos R, Foronda A, Foronda G, Maranthao R. Lipoprotein(a) levels are increased in patients with pulmonary artery hypertension (Abstr). Eur Heart J 1998; 3007
Plasma Plasminogen Activator Inhibitor-1 Activity in Normoglycemic Hypertriglyceridemic North Asian Indian Subjects: A Preliminary Case-Control Study

Rupa Sarkar, Anoop Misra, Renu Saxena, Ravindra M Pandey, Debashish Chaudhary
Departments of Medicine, Hematology, and Biostatistics
All India Institute of Medical Sciences, New Delhi

Background: Recent evidence suggests that increased activity of plasma plasminogen activator inhibitor-1, an important component of the insulin resistance syndrome, plays a crucial role in the pathogenesis of atherosclerosis.

Methods and Results: In this case-control study, relationships between plasma plasminogen activator inhibitor-1 activity, serum triglyceride levels and hyperinsulinemia were explored in 40 non-diabetic patients with primary hypertriglyceridemia (Group 1) and 40 non-diabetic normotriglyceridemic controls (Group 2) matched for potential confounders like smoking and physical activity. Mean values of fasting serum insulin levels were increased in Group 1 (p>0.05). Hyperinsulinemia was observed in 14 (17.5%) individuals in Group 1 and 11 (13.8%) individuals in Group 2. Mean plasma plasminogen activator inhibitor-1 activity in Group 1 (9.8±8.4 IU) was higher than in Group 2 (7.0±7.7 IU), though the difference was not significant (p>0.05). However, when only subjects with elevated levels of plasma plasminogen activator inhibitor-1 activity were taken into account, mean values were significantly higher in Group 1 (p<0.05). The plasma plasminogen activator inhibitor-1 activity was higher in subjects with body mass index >25 in both the groups, significantly so in males (p=0.05). Hyperinsulinemic subjects with a body mass index >25 and raised serum triglyceride levels had higher mean values of plasma plasminogen activator inhibitor-1 activity (18.42±11.15 IU) than subjects with similar characteristics and normal triglyceride levels (14.22±8.20 IU, p<0.05).

Conclusions: Though in the current study a trend for hyperinsulinemia and high plasma plasminogen activator inhibitor-1 activity was observed in hypertriglyceridemic subjects, a larger study is needed to achieve significant differences and correlations. Obese male subjects, irrespective of their lipid profile, are at risk for thrombotic events in view of their significantly higher plasma plasminogen activator inhibitor-1 values. Procoagulant tendency is further enhanced if hypertriglyceridemia and hyperinsulinemia are added on to obesity. (Indian Heart J 2001; 53: 61–65)

Key Words: Plasminogen activators, Hypertriglyceridemia, Obesity

Asian Indians have an increased tendency to develop insulin resistance syndrome (IRS) presenting with hyperinsulinemia, hypertriglyceridemia, decreased high-density lipoprotein cholesterol (HDL-c), increased very low-density lipoprotein cholesterol (VLDL-c) and visceral adiposity. Recently, there is persuasive evidence to suggest that alteration in the coagulation pathway is an important component as well. Besides hyperfibrinogenemia and alteration in the coagulation factors, increased plasminogen activator inhibitor-1 (PAI-1) has been hailed as one of the important components of IRS. A critical factor in the coagulation pathway, PAI-1 leads to thrombotic tendency when its levels are high, thus aiding in acute and chronic atherothrombotic events.

There is a close correlation between plasma PAI-1 levels and increased levels of serum triglycerides (TG), as demonstrated earlier in patients with type IV hyperlipoproteinemia. Plasma PAI-1 antigen correlated significantly with peripheral insulin resistance and fasting
plasma insulin levels. Even in people with normal glucose tolerance, fasting serum insulin levels are associated with elevated levels of plasma PAI-1 activity and other indicators of the hypercoagulable state. In addition, there was a close relationship with the other components of IRS: hypertension and high waist–hip ratio (W–HR).

Most of the studies which show an association between hypertriglyceridemia and high levels of plasma PAI-1 activity did not have a control component. In particular, matching for potential confounders such as hypertension, body mass index (BMI), and smoking was not done. Furthermore, no data are available in the native Asian Indian population predisposed to develop insulin resistance and hypertriglyceridemia.

We hypothesized, therefore, that non-diabetic north Asian Indian subjects with non-familial hypertriglyceridemia have high levels of plasma PAI-1 activity, and this is related to insulin resistance. In this matched case–control study we explored the relationship between plasma PAI-1 activity with serum levels of TG and hyperinsulinemia in hypertriglyceridemic patients and compared them with normotriglyceridemic controls.

**Methods**

This study was conducted between January 1999 and June 2000 at a tertiary care referral center in north India. Forty non-diabetic subjects in the age group of 18 to 70 years with serum TG levels greater than 200 mg% with no clinical and electrocardiographic evidence of coronary heart disease (CHD), secondary dyslipidemias, and significant pulmonary, hepatic, or renal disorders, attending medical outpatient departments and lipid research clinics were selected as cases. They were also carefully screened for the intake of anticoagulant or similar drug therapy. Forty healthy subjects selected from among the physicians and students of the hospital community, responding to a local advertisement, were selected as the control group. These subjects were in the age group of 18 to 70 years with serum TG levels of less than 200 mg%. They were selected on the basis of entry criteria defined for the cases. They were matched with the cases with respect to sex, blood pressure, and BMI. Potential confounders such as smoking and physical activity were also taken into account.

The institutional ethics committee approved the study. Informed consent was taken from all the subjects. Blood pressure was recorded in the sitting position with a mercury sphygmomanometer after 5 minutes of rest according to the standard guidelines.

**Anthropometric measurements**: Weight was measured to the nearest kilogram and height to the nearest centimeter. The BMI was calculated using the formula, BMI = weight (kg)/height(m)^2. Standard guidelines were followed for measuring the body circumferences and skinfolds. The subjects were examined in the minimum possible clothes and the same instruments of measurement were used in all the subjects. Waist circumference (WC) was measured midway between the iliac crest and the lowermost margin of the ribs. Hip circumference was measured at the maximum circumference of the buttocks using the greater trochanter as the reference point. The mean of three readings of each was taken for the calculation of W–HR. The biceps, triceps, subscapular and supra-iliac skinfolds were measured using Lange skinfold callipers. The biceps skinfold was measured at the level of the nipple line with the right arm dependent. For the triceps skinfold, the fat pad midway between acromion process of scapula and olecranon process was measured. Fat pads at the inferior angle of scapula, and superiorly on the iliac crest in the midaxillary line were measured for subscapular and supra-iliac skinfolds. All skinfolds were measured to the nearest 1 mm. A mean of three readings was recorded at each site. The same observer recorded all the anthropometric measurements to minimize the inter-observer bias. Percentage body fat (% BF) was calculated from the sum of the four skinfolds using an equation validated in Asian Indians.

**Metabolic measurements**: All the subjects underwent a glucose tolerance test after a 75 g oral glucose load, performed according to the WHO guidelines. Blood for lipid analysis was collected after a 12-hour overnight fast, while for the previous three days the subjects consumed normal diet. Total cholesterol (TC), TG and HDL-c were measured according to the method described earlier. The value of LDL-c was calculated using Friedwald’s formula: LDL-c = TC – (HDL-c + TG/5). Serum insulin assay was performed by double antibody radioimmunoassay according to the method described earlier. There was no inter-assay variation since all samples were analyzed in one assay.

**Plasma PAI-1 estimation**: Venous samples were immediately stored at –70 °C. For the estimation of plasma PAI-1 activity, enzyme immunoassay was done using a commercial kit (Diagnostica Stago, Seine, France). The reaction was taken as positive when a monoclonal anti-PAI-1
1 antibody labelled with enzyme-horseradish peroxidase was observed to bind to the anti-PAI-1/PAI-1 complex previously formed in the well of the polystyrene microplate strips. A blue colour results on incubation of the complex with the enzyme substrate and the amount of colour produced is proportional to the amount of PAI-1 originally present in the sample or standard.

**Definitions:** Central skinfold thickness indicated the sum of the subscapular and supra-iliac skinfold thickness. Peripheral skinfold thickness included a sum of the biceps and triceps skinfold thickness. A hypertriglyceridermic subject was defined as one with a serum TG level greater than 200 mg% while any value of serum TG less than 200 mg% was accepted as normal. A nonobese subject was defined as having a BMI less than 25 kg/m². Diabetes mellitus was excluded by criteria defined by the WHO. Plasma PAI-1 values greater than 7.00 IU were considered to be high. The insulin values were subdivided into four quartiles (quartile 1: 0–60 µIU, quartile 2: 61–120 µIU, quartile 3: 121–180 µIU and quartile 4: 180 µIU–max). The values of serum insulin in the last two quartiles were taken as an indication of hyperinsulinemia.

**Statistical methods:** The data were recorded on a pre-designed proforma, managed on an Excel worksheet and entries were checked several times for any possible error. Statistics for most parameters were computed by mean and standard deviation for the study and control groups. The Z-test was used to compare the difference in mean values among the two groups for all variables. For statistical significance, p values smaller than 0.05 were considered.

**Results**

Forty subjects (mean age 32.8±10.5 years) comprised the study group (Group 1), and similar numbers were taken as controls (Group 2, mean age 39.3±10.1 years).

**Anthropometric profile:** The mean BMI, WC, W–HR, all skinfolds, central and peripheral skinfolds, percentage body fat and % BF/BMI ratio did not show any significant difference between the two groups (Table 1).

**Metabolic profile:** Levels of total cholesterol and TG were significantly increased in Group 1 (p<0.01, Table 2). The level of LDL-c was also increased in Group 1 as compared to Group 2 (p>0.05) while HDL-c was significantly lower (p<0.05).

**Serum insulin:** Mean values of fasting serum insulin were increased in Group 1 (p>0.05, Table 2). Hyperinsulinemia was seen in 14 (17.5%) individuals in Group 1 and 11 (13.75%) individuals in Group 2 (Table 2). The mean values of raised serum insulin in Group 1 and Group 2 were found to be 222.0±87.2 µIU and 215.4±123.9 µIU, respectively (p>0.05). In both groups, the mean serum insulin levels in subjects with hyperinsulinemia and BMI<25 was 225.3±114.5 µIU, whereas in subjects with BMI >25 it was 202.1±94.3 µIU, (p>0.05). In both groups, the mean serum insulin levels in subjects with hyperinsulinemia and BMI<25 was 225.3±114.5 µIU, whereas in subjects with BMI >25 it was 202.1±94.4 µIU, (p>0.05).

**Plasma PAI-1:** Mean plasma PAI-1 activity in Group 1 (9.8±8.4 IU) was higher than Group 2 (7.0±7.7 IU) though the difference was not significant (p>0.05). The plasma PAI-1 activity in both groups was found to be less in those with a BMI <25 compared to subjects with BMI >25. However, the difference was significant in males (9.2±6.9 IU for a BMI >25 and 6.1±5.5 IU for a BMI <25, p=0.05), but not in females (12.8±8.9 IU for BMI >25 and 12.0±8.9 IU for BMI<25, p<0.05). Plasma PAI-1 activity was not significantly correlated to W–HR in both groups.

The mean plasma PAI-1 activity in hyperinsulinemic subjects in Groups 1 and 2 was 10.0±8.9 IU and 9.7±7.7

### Table 1. Anthropometric parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (n=40)</th>
<th>Group 2 (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index (kg/m²)</td>
<td>22.71±4.75</td>
<td>24.52±10.20</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>23.89±8.84</td>
<td>24.28±7.50</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>%Body fat/body mass index</td>
<td>1.05±0.32</td>
<td>1.04±0.34</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Biceps skinfold (cm)</td>
<td>8.59±7.26</td>
<td>10.04±8.51</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Triceps skinfold (cm)</td>
<td>14.10±8.88</td>
<td>14.04±9.93</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Subscapular skinfold (cm)</td>
<td>20.18±12.11</td>
<td>19.21±10.70</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Supra-iliac skinfold (cm)</td>
<td>20.18±12.11</td>
<td>19.21±10.70</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Subscapular-triceps skinfold ratio</td>
<td>1.62±0.59</td>
<td>1.54±0.57</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total skinfolds (cm)</td>
<td>62.96±36.16</td>
<td>62.44±31.84</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Peripheral skinfolds (cm)</td>
<td>22.70±15.81</td>
<td>24.08±16.66</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Central skinfolds (cm)</td>
<td>40.26±22.71</td>
<td>38.35±18.73</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>80.21±19.79</td>
<td>71.17±20.41</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Waist–hip ratio</td>
<td>0.89±0.08</td>
<td>0.87±0.07</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

All values in mean ± SD

### Table 2. Metabolic profile

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=40)</th>
<th>Group 2 (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting venous blood glucose (mg%)</td>
<td>86.2±11.0</td>
<td>85.5±10.0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total serum cholesterol (mg%)</td>
<td>217.1±58.9</td>
<td>218.6±41.9</td>
<td>=0.01</td>
</tr>
<tr>
<td>Serum triglycerides (mg%)</td>
<td>346±29.5</td>
<td>316±31.2</td>
<td>=0.01</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mg%)</td>
<td>34.5±5.5</td>
<td>39.6±8.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Serum LDL cholesterol (mg%)</td>
<td>124.1±47.1</td>
<td>118.1±43.9</td>
<td>=0.05</td>
</tr>
<tr>
<td>Fasting serum insulin (µIU)</td>
<td>125.5±94.3</td>
<td>120.1±25.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mean value in subjects with high fasting serum insulin* (µIU)</td>
<td>222.0±87.1(14)</td>
<td>215.4±123.8(11)</td>
<td>=0.05</td>
</tr>
</tbody>
</table>

HDL: high-density lipoprotein, LDL: low-density lipoprotein, *serum insulin >120 µIU

The values in parenthesis denote the number of subjects with hyperinsulinemia.

All values in mean ± SD
IU, respectively (p>0.05). In both groups, mean values of plasma PAI-1 activity in hyperinsulinemic subjects was higher (10.0±8.9 IU) than in normoinsulinemic subjects (9.7±8.3 IU, p>0.05). The mean activity of plasma PAI-1 in the upper two quartiles of serum insulin levels (16.7±7.4 IU) was more than that observed in the lower two quartiles of insulin values (15.7±4.6 IU, p>0.05).

When subjects with only elevated levels of plasma PAI-1 activity were analyzed, mean values were significantly higher in Group 1 (17.5±4.1 IU in Group 1 [n=20] v. 14.4±4.5 IU in Group 2 [n=20], p<0.05). However, there was no difference between the hyperinsulinemic and normoinsulinemic subjects (p>0.05). Hyperinsulinemic subjects with a BMI >25 and raised serum triglyceride levels had higher mean values of plasma PAI-1 activity (18.4±11.15 IU) than subjects with similar characteristics and normal triglyceride levels (14.2±8.20 IU, p<0.05).

Discussion

Several studies emphasize the close correlation between plasma PAI-1 activity and increased serum TG in patients with and without CHD. In a study conducted in 75 Asian Indian patients with CHD, there was a significant association between serum TG and plasma PAI-1 activity. It was concluded that hypertriglyceridemia was positively related to elevated plasma levels of PAI-1, particularly in elderly persons with CHD. The limiting factor in this study was the absence of any data regarding serum insulin levels and its correlation with plasma PAI-1 activity and serum levels of TG. Furthermore, the study group, unlike the one for the current study, was not matched with respect to smoking and hypertension, which are associated with IRS.9

In a trial carried out in normoglycemic healthy subjects, plasma levels of PAI-1 activity were strongly associated with serum TG in both men and women. Multivariate analysis revealed that serum TG had a definite positive correlation with plasma PAI-1 activity.10 Serum TG and parameters of fibrinolytic activity were related to plasma PAI-1 in 54 subjects with different types of primary hyperlipidemia.2 In a population-based study,11 and another recent trial,12 similar conclusions were reached. It must be mentioned, however, that none of the above studies were conducted in a case–control manner with satisfactory matching of confounders similar to that carried out in the current study, where significantly high activity of plasma PAI-1 was observed in the subjects having hypertriglyceridemia, when compared to normotriglyceridemic subjects.

In their study, Mykkanen et al.10 showed that in subjects with normal serum levels of TG, plasma PAI-1 activity was raised when the BMI was >25. In the current study, obese subjects, particularly males, had a significantly high activity of plasma PAI-1, regardless of their lipid profile. Plasma PAI-1 activity was significantly associated with BMI, W–HR, serum TG and several other factors in a randomly selected sample of 38-year-old healthy men.13 Though plasma PAI-1 activity is correlated with generalized obesity, visceral adipose tissue has been proposed as an important source of plasma PAI-1 in humans.14 Of note is the fact that increase in visceral adiposity is an important component of IRS. This is particularly relevant in Asian Indians, where high prevalence of visceral adiposity has been observed, and this has been correlated with levels of plasma PAI-1.15 In the present study, however, we did not observe any correlation of W–HR with plasma PAI-1 levels.

Plasma PAI-1 activity is closely regulated by, and correlated to, the serum insulin levels. In vitro studies on hepatocytes show that insulin stimulates synthesis of plasma PAI-1.16 In a controlled study carried out in 38 patients with type 2 diabetes mellitus, the plasma PAI-1 activity correlated significantly with serum insulin level. Furthermore, the highest values were found in diabetics with CHD.17

As mentioned earlier, this study was conducted strictly on normoglycemic subjects. Though the serum insulin values and plasma PAI-1 activity were found to be raised in subjects with hypertriglyceridemia, statistical significance was not reached except in obese subjects. Several studies correlating raised serum TG and raised serum insulin as components of IRS have already been carried out.4,18 However, Mykkanen et al.10 showed that insulin sensitivity is not an independent determinant of plasma PAI-1 activity. The present study also showed a considerable rise in plasma PAI-1 levels in the upper tertiles of serum insulin values in comparison to the lower tertiles. In a population-based study, plasma PAI-1 activity and fasting hyperinsulinemia correlated positively only in subjects with hypertriglyceridemia.11 Carlson et al.11 further noted that fasting serum insulin levels correlated positively with plasma PAI-1 activity in obese individuals. However, in lean subjects there was no such association. Again, there was no documentation as regards confounders such as smoking and hypertension in this study. None of these studies explores the relationship of plasma PAI-1 activity, IRS, and hyperlipidemia in Asian Indians residing in India.

However, not all workers concur with the correlation of serum levels of TG and plasma PAI-1 activity. In a controlled clinical study, the level of plasma PAI-1 was determined in 38 type 2 diabetic patients and 20 age-matched controls.
No significant correlation between serum TG level and plasma PAI-1 activity was observed.\textsuperscript{17} The authors concluded that the stronger association between plasma PAI-1 activity and serum TG levels in other studies was apparently due to correlation of hyperinsulinemia and plasma PAI-1 on the one hand and hyperinsulinemia and serum TG levels on the other, thus explaining the observed relationship between plasma PAI-1 activity and serum TG levels. Observations of Vague et al.,\textsuperscript{17} however, may also be taken to explain the correlations as observed in the current study.

Observations of the present study, therefore, suggest that in north Indian patients with hypertriglyceridemia, there is a trend for increased plasma PAI-1 activity as compared to normotriglyceridemic patients, and this persists in hyperinsulinemic subjects as well. Obese patients, in particular, regardless of their serum levels of TG, had significantly high levels of plasma PAI-1 activity. Further, the concomitant presence of all three factors (obesity, hyperinsulinemia and hypertriglyceridemia) enhances the activity of plasma PAI-1, leading further to a procoagulant tendency. Asian north Indians would be at a higher risk for hyperinsulinemic subjects as well. Obese patients, in particular, regardless of their serum levels of TG, had significantly high levels of plasma PAI-1 activity. Further, the concomitant presence of all three factors (obesity, hyperinsulinemia and hypertriglyceridemia) enhances the activity of plasma PAI-1, leading further to a procoagulant tendency. Asian north Indians would be at a higher risk for

**Acknowledgments**

The authors express their appreciation to the staff of the Department of Haematology and SRB Centre of Clinical Pharmacology, Department of Medicine, All India Institute of Medical Sciences, New Delhi including Dr I Taneja, Mr R Giri, Mr G Chand and Mrs Alice Jacob for performing various investigations, Mr RLT Taneja for performing quality control of various biochemical tests, and Miss Jyoti for typing and editing the manuscript.

**References**

Operative Outcome and Intermediate Term Follow-up of Neonatal Blalock-Taussig Shunts

K Sivakumar, K Shivaprakasha, Suresh G Rao, R Krishna Kumar
Departments of Pediatric Cardiology and Cardiac Surgery, Amrita Institute of Medical Sciences, Cochin

Background: The neonatal age group is considered to be one of the important risk factors for perioperative morbidity and mortality as well as poor long-term patency following Blalock-Taussig shunts.

Methods and Results: Out of a total of 190 patients who underwent Blalock-Taussig shunts in our institute between July 1998 and July 2000, 20 patients were aged less than 30 days and this neonatal cohort was studied retrospectively. The mean age was 18±11 days (range: 3-30 days). The mean weight of the babies was 3.1±0.7 kg, the smallest weighed 2.1 kg. The cardiac anatomy was tetralogy of Fallot with pulmonary atresia in 6, pulmonary atresia with intact ventricular septum in 3, tricuspid atresia in 5 and complex single ventricle physiology in the rest. All patients were deeply cyanotic and preoperative prostaglandin E1 was needed in 10 patients to ensure ductal patency and maintain oxygen saturations prior to the shunt operation. The mean hilar right and left pulmonary artery sizes were 3.99±0.44 mm and 3.69±0.79 mm, respectively. Three patients (15%) had significant stenosis at the site of duct insertion. The shunts were accomplished with 3.5 mm polytetrafluoroethylene grafts in 7 patients (35%) and 4 mm in the rest. The mean duration of mechanical ventilation was 2.0±2.83 days, one patient who developed bronchopneumonia needed prolonged ventilation for 14 days. The mean intensive care unit stay was 4.79±2.66 days. The mean hospital stay was 11.7±6.4 days. Five patients who developed sepsis stayed beyond 14 days. There were 3 deaths (immediate post-operative shock and possibly shunt malfunction in 1, bronchopneumonia in 1 and late shunt thrombosis at 3 months in 1). Two patients had late shunt block, one of those mentioned above and the other at 3 months secondary to infective endarteritis of the right pulmonary artery. All these infants received 4 mm grafts. All the 3.5 mm grafts were patent at follow-up. Seventeen patients were alive and well at follow-up (mean: 9 months, range: 3-21 months) with a mean resting systemic oxygen saturation of 77% (66%-95%).

Conclusions: The overall shunt patency rate after neonatal Blalock-Taussig shunt is about 80% on intermediate term follow-up. A smaller graft size (3.5 mm) does not appear to be an incremental risk factor for shunt blockade and operative mortality. (Indian Heart J 2001; 53: 66-70)

Key Words: Tetralogy of Fallot, Shunts, Congenital heart defects

The surgical creation of a systemic artery-to-pulmonary artery anastomosis to improve pulmonary blood flow in tetralogy of Fallot (TOF) was conceptualized by Blalock and Helen Taussig in 1945. The modified Blalock-Taussig shunt (BT shunt) interposes a polytetrafluoroethylene (PTFE) graft between the subclavian artery and the ipsilateral pulmonary artery and provides a controlled blood flow to the lungs, since the subclavian artery orifice of the BT shunt acts as a flow regulator. These modified BT shunts provide good palliation in many cyanotic congenital cardiac defects with reduced pulmonary blood flow.

In developing countries, the neonatal cardiac surgical program is poorly developed in many centers. Limited studies are available from India on these neonatal surgical procedures. Moreover, since febrile illnesses and diarrheal diseases are common in developing countries with higher ambient temperatures resulting in dehydration, patency rates following the modified BT shunt may be different from those of developed countries. The neonatal age group, (age less than 30 days) has been recognized as an incremental risk factor for postoperative mortality and shunt failure in studies from developing countries. Our study aimed to analyze the immediate outcome and intermediate-term follow-up results after modified BT shunts performed in neonatal age group.
Methods

A total of 190 patients with various forms of cyanotic congenital heart defects with reduced pulmonary blood flow underwent modified BT shunts over a two-year period (October 1998 to October 2000). There were 20 infants aged less than 30 days and this neonatal age subgroup (11%) formed the subject of this study. This study is a retrospective analysis based on a review of patient records.

A detailed preoperative echocardiographic evaluation was done in all patients to assess the intracardiac anatomy by the segmental approach. No infant underwent preoperative cardiac catheterization for visualization of the pulmonary arteries. High-resolution echocardiogram was performed with HP Sonos 5500 echocardiography machine using high-frequency transducers with bandwidths of 3-8 MHz and 5-12 MHz. On the echocardiogram, the entire pulmonary artery anatomy from one hilum to the other was delineated using multiple views. Z-scores were calculated for the sizes of hilar right pulmonary artery (RP A) and left pulmonary artery (LP A) from computerized nomograms for their respective body surface area, derived from the body weight and length of the infant. The other anatomic variables of interest included the size of the aortic arch, its branching pattern, presence of patent duct, site of duct insertion into the pulmonary arteries, and presence of stenosis at the site of duct insertion.

Preoperative stabilization of these sick neonates was achieved by admission in the intensive care unit (ICU), maintenance of adequate hydration, prevention of hypothermia, assessment of metabolic parameters and correction of anomalies detected, if any. Very sick infants received immediate infusions of prostaglandin PGE1 to maintain the ductal patency required for stabilization of saturation and metabolic profile. PGE1 infusions were started at initial doses of 0.05 µg/kg/min and later tapered to the lowest possible doses to maintain stable systemic saturations.

Surgery was performed using the conventional approach of posterolateral thoracotomy. Non-stretchable, thin-walled 3.5 mm or 4 mm Gore-Tex expanded polytetrafluoroethylene (EPTFE) grafts were used to create the BT shunts. The distal end of the shunt was anastomosed to the pulmonary artery through a transverse arteriotomy. The decision to use a 3.5 mm or 4 mm EPTFE graft was based on the size of the pulmonary artery seen on the operating table. The neonates were started on low doses of dopamine to maintain systemic pressure and electively ventilated for 1 day. Low-dose heparin infusions at 5-10 units/kg/hour (APTT maintained at 1.5-2 times control) were started after achieving hemostasis following the shunt surgery and continued for 48 hours till oral feeds and oral low-dose aspirin (3 mg/kg) could be started. The timing of weaning away from ventilation and extubation was based on conventional clinical, hemodynamic and radiographic findings. The babies were shifted out of the ICU after extubation, weaning away of inotropes and after initiation of first feeds. Prior to discharge, all infants had a limited echocardiographic study to document shunt patency.

After discharge, these babies were followed up once in 3 months. The parameters observed on follow-up included shunt flows, pulse oximeter saturations, and growth and development of the infant. Echocardiography was repeated during postoperative visits for the pulmonary artery anatomy, evidence of shunt site distortion of the pulmonary arteries, shunt patency, ventricular function, evidence of ventricular volume overload, and timing and planning of a definitive repair procedure.

Results

The study group comprised 20 neonates and their demographic parameters are detailed in Table 1. The body surface area was calculated from the weight and length of the neonate using standard nomograms and ranged from 0.15 to 0.29 m². A 28-day-old preterm neonate with pulmonary atresia, intact ventricular septum and duct-dependent pulmonary circulation had the lowest weight of 2.1 kg at the time of surgery.

Table 1. Patient demographics

| Number of patients in study group | 20 |
| Age in days Mean | 8.2±10.7 |
| Range | 3-30 |
| Median | 14 |
| Males:Females | 9:11 |
| Body weight Mean | 3.1±0.7 kg |
| Range | 2.1-4.7 kg |
| Body surface area Mean | 0.21±0.04 m² |
| Pulse oximeter saturation on presentation | 45±18% |
| Hilar RP A diameter Mean | 3.99±0.44 |
| Z-score of hilar RP A Mean | -0.88±0.67 |
| Range | -1.78±0.61 |
| Hilar LP A diameter Mean | 3.69±0.79 |
| Z-score of hilar LP A Mean | -0.86±0.94 |
| Range | -3.38±0.84 |

RP A: Right pulmonary artery, LP A: Left pulmonary artery

IHJ-914-00.p65 4/10/01, 11:29 AM
The intracardiac anatomy of these 20 neonates is shown in the Table 2. Based on detailed preoperative echocardiographic assessment, the anatomy was suitable for biventricular repair in 6 infants, one-and-a-half ventricular repair in one infant with pulmonary atresia, and intact ventricular septum and univentricular repair in the rest of the subgroup.

**Table 2. Intracardiac anatomy in the study group**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary atresia, intact IVS</td>
<td>3</td>
</tr>
<tr>
<td>TOF</td>
<td>2</td>
</tr>
<tr>
<td>TOF, pulmonary atresia</td>
<td>5</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>5</td>
</tr>
<tr>
<td>DOR V, VSD, pulmonary stenosis</td>
<td>2</td>
</tr>
<tr>
<td>Single ventricle, pulmonary atresia</td>
<td>2</td>
</tr>
<tr>
<td>Complex malformations, heterotaxy</td>
<td>1</td>
</tr>
</tbody>
</table>

IVS: Interventricular septum, TOF: Tetralogy of Fallot, DOR V: Double outlet right ventricle, VSD: Ventricular septal defect

All babies presented with intense cyanosis and significant systemic desaturation. Ten neonates were profoundly sick and intensely cyanosed and needed stabilization in critical care units. All these infants received immediate infusions of prostaglandin PGE$_1$ to maintain ductal patency for the stabilization of saturation and metabolic profile. PGE$_1$ infusions were started at initial doses of 0.05 µg/kg/min and later tapered to the lowest possible doses to maintain stable systemic saturations. Among the 10 neonates, 8 babies had pulmonary atresia and pulmonary circulation was maintained exclusively by the patent ductus arteriosus. The other two infants had very little antegrade flows, one had a double outlet right ventricle (DORV) and pulmonary stenosis and the other had tricuspid atresia and restrictive ventricular septal defect (VSD). The other 10 neonates underwent insertion of modified BT shunts without preoperative PGE$_1$ infusions. Four babies required preoperative ventilation to stabilize systemic saturation.

The mean size of the hilar RPA was 3.99±0.44 mm and the mean hilar LPA size was 3.69±0.79 mm. Three neonates (15%) had significant duct site stenosis of the pulmonary artery and asymmetric pulmonary artery sizes. All these babies had ductal blood flows directed into the ipsilateral pulmonary artery and modified BT shunts were performed on the contralateral side of the duct. The other 17 patients had symmetric pulmonary arteries. The size of the PTFE graft used was 3.5 mm in 7 patients (35%) and 4 mm in the rest. The mean duration of mechanical ventilation was 2.0±2.8 days; one patient needed prolonged mechanical ventilation for 14 days for extensive postoperative nosocomial bronchopneumonia. The mean ICU stay was 4.79±2.66 days and the mean hospital stay was 11.7±6.4 days. There were no instances of seroma around the graft or serous effusions in this cohort of patients. Five neonates stayed for more than 14 days due to postoperative sepsis in two and wound infection requiring surgical resutting in three. There were 2 immediate postoperative deaths (10%). One 27-day-old neonate weighing 3 kg with tricuspid atresia and restrictive VSD had a 4 mm modified BT shunt and developed severe bradycardia immediately after surgery and died, presumably due to shunt malfunction. The other baby, a 5-day-old neonate weighing 2.4 kg, again with tricuspid atresia, had a 4 mm BT shunt, developed postoperative Gram-negative septicemia with multi-organ dysfunction and died on the 14th day of surgery with a patent shunt.

All survivors were followed up once in 3 months. The mean duration of the follow-up was 9 months, and the longest follow-up was 21 months. The mean resting saturation on follow-up was 77%, ranging from 66% to 95%. There was one late postoperative death 3 months after surgery, due to acute shunt thrombosis and a marked fall in systemic saturation. This baby was a 30-day-old neonate weighing 4.5 kg at the time of surgery with tricuspid atresia and restrictive VSD and had a 4 mm modified BT shunt. There was another patient with a late shunt malfunction.

Three months after surgery, this baby with a DORV and pulmonary stenosis developed infective endarteritis with a Gram-negative non-fermenter organism. Parenteral cefotaxime and netilmicin were given for 3 months. She developed shunt occlusion, but saturation remained stable at around 70% on beta-blocker therapy. Her echocardiogram 6 weeks after discharge showed pseudoaneurysm of the RPA measuring 1.2 cm at the shunt insertion site. There was no further progression of its size on follow-up visits.

Seventeen patients (16 had patent shunts) were alive and well at follow-up. Three infants with complex malformations had mild growth and developmental delay. All 7 babies who received 3.5 mm modified BT shunts were discharged from hospital and remained well on follow-up. None of the patients had shunt revisions. One patient with tricuspid atresia underwent bi-directional Glenn anastomosis and interruption of the BT shunt. The others await definitive repair. Patients planned for univentricular repair are being followed at 3-monthly intervals with close monitoring of oxygen saturation. All patients continue to receive antiplatelet doses of aspirin to maintain shunt patency.

**Discussion**

In neonates, BT shunts offer significant palliation for a variety of cyanotic congenital malformations with duct-
dependent pulmonary circulation. Young age remains an important risk factor for poor outcome after BT shunts.6-9 The major problems we faced in these neonatal BT shunts were related to difficult ICU issues. Sudden postoperative increase in pulmonary circulation causing pulmonary congestion, longer duration of mechanical ventilation resulting in bronchopneumonia and central line-related sepsis were of major concern. These were the major reasons for prolonged stay in the ICU.

In infants less than 3 months of age, Tamisier et al.7 reported 21% early deaths and shunt failure in half of the study group. The series of 28 neonates by Moulton et al.8 had an early mortality of 11%. Ilbawi et al.9 reported 0.6% mortality following neonatal modified BT shunts in infants with an exclusive diagnosis of TOF in which the pulmonary arteries are often confluent. However, in a variety of other congenital defects including pulmonary atresia and other complex diseases, Kirklin et al.4 reported 12% mortality, reflecting the impact of pulmonary artery anatomy on the outcome. The immediate postoperative mortality in our study group is 10%. In a study of classical BT shunts by Aciniegas,5 there were 5.5% early deaths, but complex defects had an increased mortality. Our group had a variety of diagnoses, depicted in Table 1 and had hypoplastic pulmonary arteries as shown by their mean Z-scores of hilar pulmonary arteries (−0.88). In one large series of 78 neonates operated over a 13-year period, Al Jubair et al.10 reported higher adverse outcome rates when the mean PA diameter was less than 4 mm and weight was less than 3 kg. Most of our patients had smaller pulmonary arteries.

Gold et al.11 reviewed their results in 112 shunts done in 92 infants, which included neonates using 4 mm and 5 mm grafts, and reported a 21% incidence of congestive heart failure secondary to increased blood flow and 3% mortality. In the series of Tsai et al.,12 young age and smaller graft size were reported as incremental risk factors for shunt failure, but there were only 3 patients who received grafts smaller than 4 mm. Our group included grafts of size 3.5 mm and 4 mm and none of the patients were in heart failure on follow-up. A subgroup analysis of the pre- and postoperative variables was made between the 3.5 mm and 4 mm groups and is shown in Table 3. In our group, 3.5 mm grafts were used more often in younger neonates. The anatomy was similar, and both groups had a similar postoperative course. There were no deaths or shunt failures in this subgroup which received 3.5 mm grafts. However, 3 babies in the 3.5 mm graft group (comprising younger babies) developed wound infection and hence had prolonged hospital stay.

BT shunts performed in the neonatal period adversely affect the intermediate-term patency rates (up to 2 years). Kay et al.6 reported 74% freedom at 2-year follow-up in BT shunts performed in neonates compared to 90% freedom from adverse events in older infants. In our study, 2 patients had intermediate-term shunt failure, one died due to late presentation and the other secondary to infective endocarditis. Sixteen patients (80%) had a patent shunt on intermediate follow-up.

Ten neonates received preoperative PGE1 infusions to stabilize their saturations before surgery. Administration of PGE1 improves the preoperative hemodynamic and metabolic status and stabilizes the neonate. Browdie et al.3 reported the safe use of PGE1 followed by BT shunt in cyanotic neonates. In our cohort, 12 patients had a patent arterial duct. However, the duct flows were very restrictive in all patients resulting in a marked fall in oxygen saturations warranting urgent shunt surgery. All patients who received PGE1 infusions had closure of duct documented on echo-cardiography after surgery when PGE1 was discontinued. Two patients continued to have duct flows that were very small and did not result in pulmonary circulatory overload.

Three patients had significant duct site stenosis with selective duct flows into the ipsilateral pulmonary artery. In all these patients, shunts were placed on the contralateral side. The option of a combined approach of repair of

### Table 3. Relation between size of graft and variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>3.5 mm graft</th>
<th>4 mm graft</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in days</td>
<td>10.7±8.99</td>
<td>21.8±9.19</td>
<td>0.01*</td>
</tr>
<tr>
<td>Weight of patient (kg)</td>
<td>2.85±0.36</td>
<td>3.13±0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.2±0.02</td>
<td>0.21±0.04</td>
<td>0.52</td>
</tr>
<tr>
<td>Hilar RPA size (mm)</td>
<td>4.16±0.63</td>
<td>3.88±0.25</td>
<td>0.18</td>
</tr>
<tr>
<td>Z-score hilar RPA</td>
<td>-0.59±0.78</td>
<td>-1.0±0.57</td>
<td>0.2</td>
</tr>
<tr>
<td>Hilar LPA size (mm)</td>
<td>3.54±1.23</td>
<td>3.73±0.42</td>
<td>0.6</td>
</tr>
<tr>
<td>Z-score hilar LPA</td>
<td>-0.88±1.36</td>
<td>-0.8±0.63</td>
<td>0.4</td>
</tr>
<tr>
<td>Preop PGE1 requirement</td>
<td>5(71%)</td>
<td>5(38%)</td>
<td></td>
</tr>
<tr>
<td>Days of ventilation</td>
<td>2.14±0.37</td>
<td>2.84±3.43</td>
<td>0.6</td>
</tr>
<tr>
<td>Days of ICU stay</td>
<td>5±0.82</td>
<td>4.6±3.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Total hospital stay (days)</td>
<td>16.5±6.71</td>
<td>9.5±4.66</td>
<td>0.01*</td>
</tr>
<tr>
<td>Mean saturation on follow-up</td>
<td>78.1±8.6</td>
<td>76.6±7.7</td>
<td>0.77</td>
</tr>
<tr>
<td>Deaths (immediate and late)</td>
<td>0</td>
<td>3</td>
<td>#</td>
</tr>
<tr>
<td>Shunt block</td>
<td>0</td>
<td>3</td>
<td>#</td>
</tr>
</tbody>
</table>

* Small sample size, # Statistically significant
confluence stenosis and a central BT shunt through a median sternotomy was not carried out as it warrants a cardiopulmonary bypass and open heart procedure, which carries a high risk in the neonatal age. The additional cost of open heart surgery is also of concern in an emergency setting.

In this study, postoperative heparin was routinely administered to all neonates. Heparinization remains an issue of debate. In Al Jubair’s series, use of heparin improved immediate shunt function while, in a study by Mullen et al., no additional benefit of heparinization was seen. The timing of initiation of heparinization during shunt surgery is another controversial issue. In all our patients, low-dose heparinization was initiated after achieving hemostasis. Heparinization before insertion of a shunt increases the risk of seromas and serous effusions. There were no instances of seromas or serous effusions in our group. Mullen et al. have shown that there were no instances of seroma when heparinization was not initiated during surgery. These seromas were also more common when porous Dacron tube grafts were used in the past, compared to the currently used Gore-Tex EPTFE grafts. Heparinization may not be important when prosthetic materials are not used, as in the case of classical shunts in neonates. Yoshimura, in a study of classical shunts in 31 neonates over a 16-year period, reported only one instance of shunt failure. None of our neonates received classic shunts since the superiority of modified shunts over classic shunts in neonates has been shown in many studies.

One patient in this series developed infective endocarditis and non-progressive pseudoaneurysm at the shunt insertion site. Such pseudoaneurysms following shunts in young patients have been reported and can occasionally compress mediastinal structures. This patient, in spite of shunt failure, maintained adequate resting saturations and hence is on medical follow-up. These aneurysms may pose problems during definitive repair and hence are of concern.

Ideally, patients planned for single ventricular repair should have a staged approach towards definitive repair. Bi-directional Glenn is better done at around one year of age. This approach prevents volume overload of the ventricles resulting from the shunt and is a safer bet against shunt blockage. In view of cost constraints of two open heart operations in a staged single ventricle repair, we continue to follow patients to an age at which hemodynamics are acceptable for a single-stage modified Fontan procedure. However, if there is any significant fall in oxygen saturation, bi-directional Glenn surgery is planned.

**Conclusions:** Neonatal modified BT shunts in a developing country such as India offer safe and reasonable palliation with acceptable mortality for congenital complex cyanotic heart diseases with duct-dependent pulmonary circulation. The neonatal age group has a higher morbidity resulting in longer duration of mechanical ventilation and ICU stay and has a higher propensity for sepsis. The overall shunt patency rates after neonatal BT shunt is about 80% on intermediate-term follow-up. Smaller graft size (3.5 mm) does not appear to be an incremental risk factor for shunt blockage and operative mortality. Immediate postoperative low-dose heparinization, though controversial, is not associated with any major adverse events.

**References**


Left Ventricular Pacing through Coronary Sinus Tributaries: Initial Experience

SK Dwivedi, RK Saran, AK Rathi, N Tripathi, VS Narain, VK Puri
Department of Cardiology, King George's Medical College, Lucknow

Background: Left ventricular pacing is increasingly being used as a part of biventricular pacing in congestive heart failure but data on safety, feasibility, reliability and lead maturation are sparse.

Methods and Results: Seventeen patients (13 males and 4 females) with persistent symptomatic degenerative complete heart block underwent temporary left ventricular pacing by a left subclavian puncture through the coronary sinus to its tributaries using a unipolar permanent pacing lead connected to an external pulse generator. The left ventricular pacing was done for two weeks. Permanent right ventricular apical pacing was also done at the same time through a right cephalic vein cut-down or subclavian puncture and the pacing rate was kept below that of the initial left ventricular pacing rate. Pacing parameters of the left and right ventricles were assessed at the time of implantation and at two weeks. Out of 17 patients, left ventricular pacing was successful in 11 (67.7%) patients. The time taken for the total procedure was 56±18.1 min. Lead displacement was noted in one patient without loss of pacing. At the time of implant and after two weeks, left ventricular pacing threshold, impedance, R wave height and slew rate were not different as compared to right ventricular pacing. Holter recording for 24 hours revealed regular left ventricular pacing at the end of two weeks in all patients.

Conclusions: The present study shows that left ventricular pacing through coronary sinus tributaries is feasible and reliable. A cute and subacute maturation of left ventricular pacing are similar to right ventricular apical pacing. (Indian Heart J 2001; 53: 71–73)

Key Words: Pacing, Heart failure, Heart block

Conventional treatment of symptomatic bradycardia due to complete heart block (CHB) involves permanent cardiac pacing from the right ventricular (RV) apex with or without atrial pacing. Left ventricular (LV) pacing has been suggested to be more physiological but direct LV pacing has limitations due to long- and short-term problems of transarterial access, systemic embolism, stability of pacing lead and difficulty in getting an acceptable pacing threshold.1,2 Few recent reports have shown that the LV can be paced through tributaries of the coronary sinus. This method of LV pacing has recently been used as a part of biventricular pacing restricted to patients with congestive heart failure (CHF).2

Despite these encouraging reports, LV pacing through coronary sinus tributaries is still in its investigational stage. The data on safety, feasibility and reliability of LV pacing through coronary sinus tributaries are sparse. How the pacing parameters change in subsequent days and weeks is not known. The present study was done to evaluate the feasibility, reliability, safety and lead maturation characteristics of the LV free wall pacing through the coronary sinus tributaries using a unipolar pacing lead connected to the external pacemaker generator for 2 weeks in symptomatic patients of CHB.

Methods

Seventeen consecutive patients of persistent symptomatic degenerative CHB admitted for permanent RV pacing were enrolled in the present study. Patients with prior myocardial infarction (MI), LV ejection fraction (EF) of <50% on two-dimensional echocardiography, significant valvular heart disease, electrolyte abnormalities, advanced systemic illness, chronic renal failure, those receiving antiarrhythmic therapy or those who did not give informed consent for the procedure were excluded from the study.

RV pacing was done traditionally by cephalic venous cut-down or subclavian puncture from the right side and a permanent pacemaker was implanted with lead positioned...
at RV apex. At the same time, LV pacing was done by left subclavian puncture. A unipolar pacing lead (Medtronic 4024, Pacesetter E1450, K58 or Teletronics 033-443) with trimmed tines was advanced through the coronary sinus ostia by reshaping the stylus in a smooth J curve at distal 3-4 cm. Once in the coronary sinus, the lead was advanced to the lateral aspect of the heart. The stylus was then reshaped by an angulation of 60° in the distal 0.5-1 cm and coronary sinus tributaries were entered. Once in a desired tributary, the lead was advanced to a wedge position using a straight-end stylus. Lead entry was primarily attempted in an anterolateral or lateral tributary, failing which the posterolateral or inferior tributary was chosen. A satisfactory lead position was defined as stable pacing with an acute pacing threshold of <2 V without diaphragmatic stimulation. LV pacing was done in the unipolar mode using an external pacemaker by connecting the negative terminal of the pacemaker to the lead and the positive (anodal) terminal to the subcutaneous plane at the left subclavian entry site by a metallic clip. The LV was paced at 5 V with a pulse width of 0.5 msec and pacing was done through this lead for 2 weeks. The LV pacing rate was kept at 70 bpm or 10 beats higher than the inherent rate, whichever was more. Permanent RV (apical) pacing was done in the VVI mode at a heart rate of 50 bpm. A 24-hour Holter recording was done at the end of two weeks to assess the reliability of pacing by the LV lead. Patients were discharged on permanent RV pacing at a rate of 70 bpm after removing the coronary sinus lead.

Parameters assessed at the time of implant and at the end of two weeks of LV pacing were: (1) success rate in achieving stable LV pacing through the coronary sinus as defined above; (2) coronary sinus pacing lead stimulation threshold (V), R wave height (mV), pacing impedance (ohm) and slew rate of right- and left-sided ventricular pacing lead; and (3) reliability of LV pacing through a coronary sinus tributary assessed by continuous monitoring in the intensive coronary care unit for two days, followed by ECG recording once daily for 10 days and finally, Holter monitoring for 24 hours before removing the coronary sinus lead.

Results

Seventeen patients (13 males; mean age 58.6±8.6 years) with symptomatic CHB formed the study group. LV pacing through a coronary sinus tributary was successful in 11 patients (67.7%). Inability to pace the LV was mainly due to an unacceptable acute threshold (>2V) at the time of implant (3 patients) and inability to enter the desired coronary sinus tributary (2 patients). The total procedure time for coronary sinus LV pacing was 56±18.1 min (20-220 min) in all patients and 30±6.5 min (20-68 min) in the last 5 patients who underwent a successful procedure (Table 1). The LV was paced through the anterior or anterolateral tributary in 8 and posterolateral or inferior tributary in 3 patients.

Table 1. Details of coronary sinus pacing

<table>
<thead>
<tr>
<th>Total no. of patients</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful coronary sinus pacing</td>
<td>11 (64.7%)</td>
</tr>
<tr>
<td>Total procedure time</td>
<td>56±18.1 min (20-220 min)</td>
</tr>
<tr>
<td>Procedure time in last 5 patients</td>
<td>30±6.5 min (20-68 min)</td>
</tr>
<tr>
<td>Causes of failure</td>
<td></td>
</tr>
<tr>
<td>Inability to hook CS</td>
<td>none</td>
</tr>
<tr>
<td>Inability to enter CS tributary</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Inability to achieve stable pacing and diaphragmatic stimulation</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Inadequate threshold (&gt;2V)</td>
<td>3 (17.7%)</td>
</tr>
<tr>
<td>In-hospital complications of LV pacing</td>
<td></td>
</tr>
<tr>
<td>Lead displacement (without pacing loss)</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>Loss of pacing after 2 weeks</td>
<td>none</td>
</tr>
</tbody>
</table>

While in the hospital, one patient experienced lead displacement (as diagnosed by increase in pacing threshold from 0.9 V to 2.3 V along with diaphragmatic stimulation) with persistent LV pacing. There was no episode of loss of pacing during the observation period in any of the 11 patients. Holter recording for 24 hours at 2 weeks revealed persistent LV capture by a coronary sinus pacing lead in all patients. A return to normal sinus rhythm was observed in 6 patients during hospitalization (during coronary sinus pacing) and the pacing rate was increased by 10 bpm above the inherent sinus rhythm in all these patients. Removal of the coronary sinus lead after 2 weeks of LV pacing was easy and uneventful.

Lead parameters at the time of implant, i.e. pacing threshold (0.7±0.5 v. 0.9±0.3 V), impedance (773±54 v. 704±69 ohm), R wave height (8.9±0.89 v. 9.2±6.3 mV) and slew rate (3.1±1.2 v. 2.8±2.1 mV/sec) were similar in both LV and RV pacing sites, respectively. A threshold of <1 V was obtained in 8 patients (72.6%) with coronary sinus leads as compared to 10 (90.9%) patients with RV leads. Lead maturation parameters at the end of 2 weeks, i.e. pacing threshold (0.9±0.5 v. 1.1±0.4 mV), and impedance (839±73 v. 950±88 ohm) were comparable on both sides (Table 2).
Table 2. Acute and subacute pacing parameters of LV and RV pacing

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LV pacing</th>
<th>RV pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing threshold (V)</td>
<td>0.7±0.5 (0.2–1.6)</td>
<td>0.91±0.3 (0.1–1.5)</td>
</tr>
<tr>
<td>acute</td>
<td>2 weeks</td>
<td>2.8±1.2 (0.3–2.1)</td>
</tr>
<tr>
<td>Impedance (ohm)</td>
<td>0.7±0.5 (0.2–1.6)</td>
<td>1.1±0.4 (0.3–2.2)</td>
</tr>
<tr>
<td>acute</td>
<td>2 weeks</td>
<td>773±54 (630–960)</td>
</tr>
<tr>
<td>R-wave height (mV)</td>
<td>8.9±49 (6–24)</td>
<td>9.2±6.3 (7–26)</td>
</tr>
<tr>
<td>2 weeks</td>
<td>839±73 (710–1088)</td>
<td>950±88 (690–1210)</td>
</tr>
<tr>
<td>Slew rate (V/sec)</td>
<td>3.1±1.2</td>
<td>2.8±1.2</td>
</tr>
</tbody>
</table>

Discussion

The present study shows that LV pacing through coronary sinus tributaries is feasible and safe. LV pacing was successful in 67.7% of our patients even without a special preformed pacing lead and long guiding sheath. The lower success rate may be due to the initial learning curve, difficulty in entering the cardiac veins and obtaining a reasonable threshold. A similar success rate of 53.3% has been reported by Daubart et al. with a regular pacing lead. However, with the use of special preformed pacing leads and long guiding sheath the success rate has been shown to be 81.8%.

Acutel lead parameters of the LV and RV were comparable in the present study. An acute pacing threshold of <1 V was obtained in 72.6% of our patients which is comparable to the pacing threshold of 1.18±0.8 V obtained by Daubart et al. However, lower acute pacing threshold of 0.8±0.2 V and a greater R-wave height with specially designed coronary sinus pacing lead has been reported earlier. The subacute pacing threshold at 2 weeks was satisfactory and similar in the RV and LV pacing groups in our study. Similar long-term results were obtained by previous workers. The R-wave height was similar in LV and RV pacing in our study group. Impedance and slew rates were also similar in RV and LV pacing. This suggests that maturation of LV pacing through coronary sinus tributaries is similar to RV apical pacing.

Permanent LV pacing through the coronary sinus has been anecdotally reported when passage of a lead through the right atrio-ventricular valve is not feasible due to underlying anatomical abnormalities. Recently, its application has been extended, as a part of biventricular pacing, to patients with dilated cardiomyopathy with electrocardiographic evidence of intraventricular conduction defect. In such patients, it has been shown to improve the cardiac hemodynamics in symptomatic patients categorized as NYHA Classes II and III. However, in such patients, it is not used for bradycardia support but to produce a near-synchronized biventricular contraction for obtaining a higher cardiac output.

Isolated LV pacing may prove to be hemodynamically superior, since RV pacing is shown to produce a left bundle branch block pattern, which is associated with an abnormal sequence of LV activation, resulting in compromised LV function in the short- as well as long-term. In another recently reported study in a canine model of cardiomyopathy, LV pacing through the coronary sinus has been shown to produce improved contractility as compared to both, RV apical and biventricular pacing. This provides evidence that chronic pacing from an LV site in patients with CHB may be hemodynamically superior to RV apical pacing. However, there are no human studies where LV pacing has been performed for bradycardia support as the only pacing mode in patients with CHB. Further studies can be planned to see the long-term benefit of this mode of pacing on LV function.

References

4. Rosenthal E, Qureshi SA, Crick JC. Successful long term ventricular pacing via coronary the sinus after the Fontan operation. PACE 1995; 18: 2103–2105
Efficacy and Safety of Carvedilol in Infants with Dilated Cardiomyopathy: A Preliminary Report

Naomi Gachara, Suja Prabhakaran, Shardha Srinivas, Farida Farzana, Usha Krishnan, Maully J Shah
Division of Pediatric Cardiology, Institute of Cardiovascular Disease, Madras Medical Mission, Chennai

Infants with dilated cardiomyopathy (DCM) often have clinical symptoms of severe congestive heart failure (CHF) despite standard therapy with digoxin, diuretics and angiotensin-converting enzyme (ACE) inhibitors.1–5 Orthotopic heart transplantation is now an accepted therapeutic option for patients with end-stage heart failure.6–9 However, long-term results of this procedure are unknown and there is a lack of donor organs in many parts of the world. Also, despite having severe symptoms of CHF, infants with DCM may show spontaneous improvement in cardiac function. "Bridging" strategies include the use of aggressive medical management, extracorporeal membrane oxygenation, and mechanical ventricular assist devices. The beneficial use of selective beta receptor blockers (e.g. metoprolol) in the treatment of children with DCM has been described.10–11 This report reviews the efficacy and safety of carvedilol in infants with DCM in whom the symptoms of CHF were refractory to conventional medical therapy. Carvedilol is a nonselective beta-blocker with alpha, blocking and anti-oxidative properties. Its use in adults with CHF has been widely investigated.12–16 These data can be readily extrapolated to older children with DCM but its use in infants (<2 years of age) with DCM has not been reported.

Methods

Study population: From October 1998 to October 1999, 8 patients from the 31 pediatric patients with DCM referred to our institution were selected for the study based on the following inclusion criteria: (1) DCM; (2) age less than 24 months; and (3) poor response to treatment with conventional therapy. Conventional therapy was defined as treatment with digoxin (10 µg/kg/day), diuretics (furosemide 3–4 mg/kg/day, spironolactone 3–4 mg/kg/day) and ACE inhibitor (captopril 3 mg/kg/day) for at least 1 month prior to initiation of carvedilol. Poor responders were identified as those patients who continued to have severe clinical symptoms of CHF despite conventional therapy.

Background: Carvedilol has proven to be beneficial in a majority of adult patients with congestive heart failure. Although the experience from adult patients may be extrapolated to older children, symptomatic infants remain a subset for whom dosage, safety and efficacy need to be established. The purpose of this study was to assess whether treatment with carvedilol is efficacious and safe for infants with dilated cardiomyopathy who do not show satisfactory clinical improvement despite treatment with conventional medications.

Methods and Results: Eight infants with dilated cardiomyopathy (ejection fraction<30%) who were symptomatic despite tailored treatment with decongestive medications, were enrolled in the study. Echocardiographic findings and heart failure symptom scores were analyzed before and after starting carvedilol. Patients were hospitalized and monitored for side-effects during up-titration of carvedilol. At a follow-up of 4.5±2.2 months, patients receiving carvedilol showed a significant improvement in the left ventricular ejection fraction (38.5±11% v. 24.4±5%), and heart failure symptom score (p<0.05). No adverse events related to carvedilol administration occurred. There were no deaths.

Conclusions: Carvedilol is well tolerated in infants with dilated cardiomyopathy and there is significant improvement in their functional status. Optimal timing of starting therapy, dosage and long-term effects need to be investigated with multi-institutional trials. (Indian Heart J 2001; 53: 74–78)

Key Words: Carvedilol, Cardiomyopathy, Heart failure
signs and symptoms of CHF and no significant improvement in left ventricular ejection fraction (<30%) and/or fractional shortening.

**Study protocol:** All patients underwent a physical examination, routine clinical laboratory tests (including complete blood count and blood biochemistry), chest X-ray, electrocardiogram (ECG), and echocardiogram prior to starting carvedilol and at follow-up. In addition, 24-hour Holter monitoring was performed at follow-up. Echocardiographic studies included M-mode, two-dimensional and Doppler echocardiographic variables. Estimates of left ventricular function included ejection fraction (EF) measured from the apical 4-chamber view using Simpson’s rule and fractional shortening (FS) measured from the parasternal short axis projection. All measurements were obtained in sinus rhythm as a mean of 3 consecutive beats. The degree of mitral valve insufficiency was classified as: grade I (mild), grade II (moderate), and grade III (severe). ECG parameters that were evaluated included heart rate, presence of arrhythmias, and measurement of electrocardiographic intervals. The results of 24-hour Holter monitoring were analyzed for the maximum, minimum and average heart rate on carvedilol as well as the presence of arrhythmias. The protocol for starting carvedilol was extrapolated from studies in adults with CHF. All patients were hospitalized during the starting and up-titrating of carvedilol. An initial dose of 0.1 mg/kg/dose twice daily was started. The up-titration regimen consisted of doubling the dose every 24 hours until a dose of 0.8 mg/kg/day was achieved when the dose was increased to a mean of 1 mg/kg/day, if tolerated (range: 0.7 mg/kg/day–2 mg/kg/day). Heart rate and blood pressure were monitored at 4-hourly intervals and one hour prior to and one hour after the carvedilol dose during hospitalization.

As all the patients in the study group were <2 years of age, NYHA class could not be determined. Instead, a heart failure symptom scoring system was designed to assess the clinical status of the patients. Parents were given a questionnaire to describe their child’s symptoms and the frequency of their occurrence (Table 1) prior to starting carvedilol and at follow-up. A higher score was proportional to increased severity of symptoms.

**Statistical analysis:** Data are expressed as mean±SD, range or percentage. Comparison between groups was made by the student’s t-test. Differences were considered significant for p<0.05.

**Results**

**Patient characteristics:** Eight patients fulfilled the criteria required to be enrolled in the study of which 6 were male and 2 female. The age at which carvedilol was started was 11±6.8 months (range 2.5–23 months, median 9.5 months) and the weight of the patients was 6.9±1.8 kg. Patients were evaluated frequently, with the most recent follow-up at 4.5±2.2 months (range: 2–9 months, median 4 months) after commencement of carvedilol. Seven of the eight patients had idiopathic dilated cardiomyopathy. None of them had clinical evidence of myocarditis. The remaining patient had DCM secondary to an anomalous left coronary artery arising from the pulmonary artery (ALCAPA). He continued to have depressed left ventricular function after surgical correction with a transpulmonary artery baffle. Individual patient characteristics are listed in Table 2.
Drug tolerability: During titration of carvedilol, no patient had any untoward events. The dose of carvedilol used was 1.08±0.4 mg/kg/day (range: 0.7–2 mg/kg/day, median 1 mg/kg/day). Patients continued to receive concomitant therapy with digoxin, diuretics and captopril. The dose of captopril was reduced by 20% during initiation with carvedilol.

ECG parameters, heart rate and arrhythmias: There were no significant changes in ECG parameters (PR interval, QRS and QTc duration) before and after carvedilol therapy. Holter monitoring was performed in 6 of 8 patients on carvedilol. The heart rate response is shown in Table 3.

**Table 3. Analysis of 24-hour Holter monitoring in six patients receiving carvedilol**

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Min. HR</th>
<th>Ave. HR</th>
<th>Max. HR</th>
<th>Arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>104</td>
<td>135</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>103</td>
<td>138</td>
<td>179</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>84</td>
<td>119</td>
<td>154</td>
<td>PVC (0.02%)*</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>96</td>
<td>126</td>
<td>PVC (4%)</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>153</td>
<td>179</td>
<td>NS-SVT</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>100</td>
<td>166</td>
<td>Nil</td>
</tr>
</tbody>
</table>

* % of rhythm, #: number, Min.: minimum, Ave.: average, Max.: maximum, HR: heart rate, PVC: premature ventricular contractions, NS: non sustained, SVT: supraventricular tachycardia

Patient #4 had ventricular arrhythmias that accounted for 14% of total beats recorded on the initial 24-hour Holter monitoring. This included frequent single ventricular ectopic beats and non-sustained ventricular tachycardia. After increasing the dose of carvedilol to 2 mg/kg/day, ventricular arrhythmias decreased to 4% of total recorded beats. Patient #5 had 4 episodes of non-sustained supraventricular tachycardia.

**Effects on echocardiographic estimates of LV function:** The LVEF improved from 24.4±5% (range: 14%–30%, median 25.5%) to 38.5±11% (range: 26%–55%, median 33.5%) after starting carvedilol (p=0.01) (Fig. 1). Four patients showed an increase of LVEF >10%. There was only a marginal increase in the LVFS from 12.2±6.6 (range: 4%–16%, median 10.5%) to 17.9±8.7% (range: 4%–33%, median 17.4%) (p=0.07). The LV end-diastolic dimensions (LVEDD) did not change significantly (LVEDD pre-carvedilol treatment 4.8±0.72 cm; post-carvedilol treatment 4.5±0.8 cm). There was no significant change in the degree of mitral regurgitation after starting carvedilol. Patient #4 had a deterioration in the estimated FS. In addition, there was evidence of spontaneous echocardiographic contrast in the left atrium and left ventricle of this patient, indicating severely diminished function.

**Effects on functional status:** Five of the eight patients are completely asymptomatic after starting carvedilol (Table 1). Of the three who are symptomatic, 2 patients have mild symptoms (scores 2 and 4 out of 14). Only one patient (patient #4) required hospitalization for further management of congestive heart failure. Six of the eight patients have demonstrated an average weight gain of 6% (range 2%–18%) over a period of 4.6±2.2 months after starting carvedilol (Fig. 2). Patient #4 has failed to thrive and patient #1 has not shown any increase in weight over a 2-month follow-up period.

**Discussion**

To the best of our knowledge, this is the first published study describing the effects of carvedilol in very young children.
with DCM. Carvedilol, is a third-generation beta-1, beta-2, and alpha-1 blocker with ancillary properties. The mechanisms of action of carvedilol in CHF include reversal of adrenergic-induced ventricular remodelling, improvement in intrinsic ventricular function, vasodilation, decreased stimulation of neurohumoral systems and antioxidant effects. The use of carvedilol has been shown to produce reduction of mortality and improvement in symptoms in adults with heart failure. Our study shows that at least the latter effects are reproduced in children with DCM.

**Tolerability of carvedilol:** The primary finding of this study was that carvedilol was tolerated by all patients. Specific complications such as profound bradycardia, hypotension, hypoglycemia or worsening heart failure were not encountered. The dose of captopril was empirically decreased by 20% due to its potential for producing hypotension because of the combined vasodilatory effects of carvedilol and ACE inhibitors. Hyponatremia, a recognized predictor for risk of adverse events during commencement of carvedilol was not encountered in any patient. All infants were hospitalized during initiation and titration of carvedilol.

**Concomitant medical therapy:** Digoxin, diuretics and captopril were continued in all patients receiving carvedilol. The mechanisms of action of vasodilatory effects of carvedilol and ACE inhibitors are different. Experimental studies have shown that vasodilation by carvedilol is mediated by alpha, receptor blockade and carvedilol does not antagonize vasoconstriction induced by angiotensin II. While the short-term vasodilatory properties of carvedilol have been established, some studies indicate that with time, there appears to be an attenuation or even loss of its acute vasodilator properties. For this reason, we chose to continue the concomitant use of ACE inhibitors and carvedilol. The dose of other anti-CHF medications was not increased after starting carvedilol in any patient.

**Effects on functional status:** Carvedilol significantly lessened the symptoms of heart failure as assessed by the patient's family using the symptom score questionnaire and by the clinician. Five of the 8 patients were completely asymptomatic at a median follow-up of 4 months (range: 2–9 months). Patient #4 was the most ill in this cohort. Despite lack of improvement in LVEF, his symptom score decreased from 1.4 to 6 after carvedilol. He was also the only patient in the study who was hospitalized (3 hospitalizations over a period of 6 months) for the treatment of acute exacerbation of CHF after starting carvedilol. Four patients were referred for heart transplantation evaluation and three were removed from transplant consideration because of their favorable response to carvedilol. Unique to infants is the effect of increased metabolic demands on nutritional status and weight gain. In this study, 6 of 8 patients demonstrated an average weight gain of 6% (range 2%–18%) over a period of 4.6±2.2 months after starting carvedilol. Patient #4 lost 0.5 kg over 4 months and patient #1 did not show any increase in weight over a 2-month follow-up period. The median weight percentile for age is 50% (range: 30%–90%). All patients were able to feed orally and nasogastric tube feeding was not required in any patient.

**Left ventricular size and function:** Several studies have demonstrated a favorable effect of carvedilol on LV dimensions, shape and LV systolic function. Even though, in the present study, the duration of carvedilol therapy was relatively short, there was improvement in the LVEF from 24.4±5% to 38.5±11% over 4.5±2.2 months. There was also a marginal improvement in the LVFS but it did not reach statistical significance. The improvement in LVEF is comparable to that reported in children with DCM treated with a selective beta blocker. The natural history of DCM in children is quite variable with the potential for spontaneous improvement in LV function. It is possible that some patients in this study may have had an improvement in LVFS and EF with a longer period of conventional therapy alone.

**Mortality:** There were no deaths in this group of patients during the study period. However, the total number of patients is small and the follow-up period not long enough to determine the impact of carvedilol on the survival of children with DCM. Currently, no comparative data are available in the pediatric literature.

**Effect on heart rate and ventricular arrhythmias:** As expected, there was a significant decline in heart rate after starting carvedilol (p<0.05). A slower heart rate may ameliorate ventricular filling and decrease myocardial energy consumption. Only one patient in the study group showed ventricular arrhythmias on Holter monitoring. The frequency of ventricular ectopy decreased after increasing the dose of carvedilol. Carvedilol may have an additional beneficial effect on the reduction of ventricular arrhythmias.

**Study limitations:** Study limitations include a small cohort of patients, a relatively short follow-up period, and lack of blinding. Another limitation is the lack of hemodynamic data from cardiac catheterization. The optimal dose of carvedilol has been extrapolated from the adult literature as there are no established guidelines for
pediatric dosage. Comparable improvement might have been obtained with other beta blockers such as metoprolol, but this was not tested as the study was specifically designed to investigate the efficacy and safety of carvedilol.27

Conclusions: The results of the present study indicate that carvedilol is tolerated well in very young patients with DCM and there is significant improvement in the functional status and LVEF in patients not responding to conventional therapy. Although the optimal treatment for DCM in children is not known, the addition of carvedilol to the armamentarium of anti-failure strategies may improve symptoms, ventricular function and survival. Patient selection criteria, optimal timing of carvedilol therapy, optimal dosage and its long term effects need to be investigated with multi-institutional trials and a larger number of patients.

References

Percutaneous Transluminal Coronary Angioplasty with Stenting of Anomalous Right Coronary Artery Originating From Left Sinus of Valsalva Using the Voda Guiding Catheter: A Report of Two Cases

Tarun K Praharaj, Gautamananda Ray
B.M. Birla Heart Research Centre, Calcutta

Coronary arteries of anomalous origin are uncommon and found in only 0.2%–1.2% of patients undergoing percutaneous transluminal coronary angioplasty (PTCA).1–3 Anomalous origin of the right coronary artery (RCA) from the left sinus of Valsalva (LSOV) has been found in 6%–27% of patients with coronary anomalies4 and in 0.02%–0.17% of coronary angiograms.5 Although clinically thought to be a benign anomaly, it can cause angina pectoris or myocardial infarction even in the absence of any distinct atherosclerotic lesion.6 At times, it can lead to faintness, ventricular fibrillation and sudden cardiac death.7 Anomalies cause technical problems during coronary angiography as well as during PTCA. There are few reports of PTCA of anomalous coronary arteries.8–12 We report two cases of successful stenting of anomalous RCA originating from the LSOV using the Voda guiding catheter.

Case Report

Case 1: A 53-year-old male was admitted to our center with a clinical diagnosis of crescendo angina of recent onset. Coronary angiography revealed 70%–80% long segment stenosis (16 mm) of the mid-RCA. The left circumflex and the left anterior descending artery were free from any disease. The 3 mm diameter-sized RCA was anomalous and originated from the LSOV (Fig. 1). The anomalous RCA lay anterior to the left main coronary artery and took a caudal anterior course between the great vessels before it continued on its normal course into the right atrioventricular groove. The left ventricular function was normal with a left ventricular ejection fraction (LVEF) of 64%. The anterior location of the ostium in the left coronary cusp with tortuous proximal portion of the artery with its caudal anterior course posed specific problems for cannulation. Diagnostic right coronary angiogram was done using a left Amplatz II catheter (Fig. 2) and anomalous origin of RCA from the LSOV was observed. The patient was re-admitted 2 weeks later for PTCA of the RCA because he remained...
symptomatic despite medical treatment. The artery could not be cannulated even after using different catheters including the Amplatz catheter. Finally, the RCA was selectively cannulated by Voda Left 8 F guide catheter (inner lumen diameter 0.080", Boston Scientific Corporation, Minnesota) (Fig. 3). The RCA stenotic lesion was successfully crossed with a 0.014" Hi-torque intermediate wire (Advanced Cardiovascular System, California), and dilated with a 3×20 mm Rocket balloon (Advanced Cardiovascular system, California) (Fig. 4). After predilatation of the narrowed segment, a 3×18 mm MultiLink stent (Advanced Cardiovascular System, California) was deployed at 16 atm. A final diagnostic angiogram showed an excellent angiographic result (Fig. 5). The immediate post-procedure stay of the patient was uneventful and he was discharged three days later on regular calcium channel blockers, aspirin and ticlopidine (for 6 weeks). The patient continued to remain asymptomatic with a good quality of life on one-year follow-up.

**Case 2**: A 56-year-old male presented with a clinical diagnosis of effort angina of recent onset with diabetes and hypertension. His coronary angiography revealed a normal left main coronary artery and left anterior descending artery. However, the left circumflex artery was a small caliber vessel, totally occluded in its mid-segment and filled through collaterals from the left anterior descending artery. Mid-RCA had a 70%-80% long segment narrowing with subtotal occlusion in its distal segment. The distal RCA was
seen to be filled through collaterals from the left anterior descending artery. The RCA (3 mm diameter) originated from the LSOV (Fig. 6) and passed between the pulmonary artery and aorta to reach the right atrioventricular groove. Thereafter it followed a normal course. The LVEF by two-dimensional echocardiography was 52%. There was mild hypokinesia of the inferior wall. The anomalous RCA had an ostium located anteriorly and superiorly and could not be cannulated with Judkin, Multipurpose and Amplatz catheters. However, cannulation was easily possible with a Voda 8 F guiding catheter (Fig. 7). The long segment narrowing in mid-RCA and the subtotally occluded distal RCA were successfully crossed with a 0.014” Hi-torque intermediate wire and dilated with a 3×20 mm Rocket balloon. The lesion in the mid-RCA was successfully dilated at 10 atm and the distal segment was stented after predilatation, using a 3×15 mm MultiLink stent at 16 atm (Fig. 8). The final diagnostic angiogram revealed excellent result (Fig. 9). A totally occluded left circumflex artery was successfully crossed with a 0.014” Hi-torque intermediate wire and predilated using a 2.5×20 mm balloon and a 2.5×15 mm MultiLink stent was deployed at 12 atm with good angiographic result. The immediate post-procedure stay of the patient was uneventful and the patient was discharged on regular medications. He remained asymptomatic at follow-up after 7 months.
Discussion

PTCA in patients with an anomalous RCA is technically challenging. It demands a high degree of awareness, and complete evaluation of the coronary artery anatomy and distribution in order to avoid complications. The complication rate of coronary arteriography and PTCA is related to the duration of the procedure. Topaz et al. have described various aspects of orifice configuration, anatomy of the artery, location of atherosclerotic lesions and also guiding catheter selection. Proper guiding catheter selection decreases procedure time in PTCA involving anomalous coronary arteries and thus increases success rate. In both cases, we were able to cannulate the anomalous RCA using the Voda guiding catheter. In the first case, the initial angiography was done using the left Amplatz catheter. However, during PTCA, the cannulation was not possible with the Amplatz catheter. Use of the Voda guiding catheter in both cases provided easy cannulation with enough back-up support. The choice of the Voda guiding catheter was based on its curvature, large area of support and location of the artery just opposite to the left ostium. It provided the maximum stable support required for the smooth passage of the balloon as well as the stent. The tip of the catheter sits well in the anomalous vessel and the secondary curve rests stably against the opposite aortic wall. The anatomical course of the anomalous RCA in both our cases corresponds to the course described by Ilia. Usually, the anomalous RCA originating from the LSOV almost invariably follows a similar course. Thus, it appears that the Voda guiding catheter may be the best for PTCA of a coronary artery with similar anomaly.

Several techniques have been reported for PTCA in an anomalous RCA. However, we could cannulate the anomalous RCA in both our cases with relative ease and got good back-up support using the Voda guiding catheter. Thus, after careful study of the course of the anomalous artery, location of the lesion and selective use of the Voda guiding catheter, angioplasty and stenting can be performed in patients with an anomalous RCA originating from the LSOV with excellent results.

References

Acutely respiratory failure is a major cause of postoperative morbidity and mortality in cardiac surgical intensive care units. This condition may require the administration of high concentrations of oxygen, which can itself be toxic and cause further lung damage. Mechanical ventilation in the prone position and its positive effect on gas exchange was described more than 25 years ago but it still remains a relatively under-used technique. Recent literature not only proves its positive results in improving oxygenation but also advocates its early application rather than using it as a last resort.1

Experience of prone mechanical ventilation in postoperative cardiac surgical patients is limited.2 We report the case of an obese male patient who underwent elective coronary artery bypass grafting (CABG) and had low PaO2 in the postoperative period.

Case Report

A 49-year-old male patient weighing 103 kg, with a body surface area of 2.07 m² was scheduled for elective CABG. The patient was a chronic smoker with a history of hypertension for the past eight years. On physical examination, the chest was clear. X-ray chest (PA view) showed normal lung fields. Pulmonary function tests showed values above 75% of the predicted values. Forced vital capacity (FVC) was 3 L, forced expiratory volume in one second (FEV1) was 2.61 L, peak expiratory flow rate (PEFR) was 6.49 L and forced expiratory flow25–75 (FEF25–75) was 2.78 L. Two-dimensional echocardiogram revealed inferior and lateral wall hypokinesia with a left ventricular ejection fraction (LVEF) of 0.35. Routine cardiac medication in the form of oral atenolol and isosorbide dinitrate was continued till the morning of the surgery. Oral lorazepam 2 mg was given on the night prior to surgery. Premedication one hour prior to surgery included intramuscular morphine sulphate and oral lorazepam. The following parameters were monitored: continuous two-lead (II and V5) ECG; intra-arterial blood pressure; pulmonary artery pressure and thermodilution cardiac output; end-tidal carbon dioxide; rectal temperature; and urine output. Anesthesia was induced with intravenous fentanyl, midazolam, thiopentone sodium and pancuronium bromide, and the trachea was intubated with a 9.0 mm cuffed orotracheal tube. Nitroglycerine infusion was used to control arterial blood pressure.

Cardiopulmonary bypass was instituted at tepid
temperature, allowing the rectal temperature to drift up to 32°C, using a membrane oxygenator, roller pump, crystalloid prime, blood cardioplegia and pulsatile flow between 2.4 and 3.8 L/min/m². The left internal mammary artery was anastomosed to the left anterior descending artery, the radial artery to the right coronary artery and the reverse segment of the saphenous vein graft to the first obtuse marginal artery. Pulsatile flows were maintained between 2.4 and 3.28L/min/m² and perfusion pressure was maintained in the range of 50 to 70 mmHg. The patient remained hemodynamically stable during the course of the surgery. The duration of surgery was 4 hours and 40 minutes, with a cardiopulmonary bypass time of 68 minutes and aortic cross-clamp time of 45 minutes. Alpha stat pH management was used and arterial blood gas reports were within normal limits intra-operatively. The patient was shifted to the recovery room with a negative fluid balance of 700 ml.

The patient was ventilated electively by volume-controlled ventilation with a Servo 300 ventilator (Siemens, Elema, Solna, Sweden). On the first day, PaO₂ was 58.8 mmHg at a FiO₂ of 1.0, and chest X-ray showed haziness in both the lower lung zones. Bronchoscopic suction was done and repeated after 4 hours. Positive end-expiratory pressure (PEEP) was gradually increased to 12.5 cmH₂O. Subsequently, the mode of ventilation was changed to pressure-controlled inverse-ratio ventilation with full sedation using midazolam and muscle relaxation with vecuronium bromide. The patient remained hemodynamically stable without any inotropic support. Cardiac enzymes and ECG were normal, but there was no improvement in the PaO₂. He was then ventilated through the volume control mode in the prone position, on three occasions—on day 2, day 3 and day 5 of surgery for 8, 6 and 8 hours, respectively. Four attendants turned the patient from the supine to the prone position. During this period, he remained hemodynamically stable and showed significant improvement in PaO₂ following all three occasions of prone ventilation. The PaO₂ increased from 57.8 to 249.7 mmHg on the first occasion, from 48.7 to 194.6 mmHg on the second and from 62.5 to 199.7 mmHg on the third occasion at an FiO₂ of 1.0. The shunt fraction (Qva/Qt) decreased from 43.6% to 7.2% on the first occasion and from 46.7% to 12.5% during the second. Due to the prone position, the patient developed swelling over the lips and left eyelid, and subconjuctival hemorrhage in the left eye on the third occasion, which resolved on its own in two days. The total negative fluid balance was 6.5 L by day 7 postoperatively. Chest X-ray showed haziness in the lower and mid-zones initially which cleared by postoperative day 6. Nutrition was maintained parenterally from postoperative days 2 to 8. The patient was extubated on postoperative day 8 at an FiO₂ of 0.4 and PaO₂ 98.4 mmHg, transferred out of the intensive care unit on postoperative day 10 and from the hospital on postoperative day 18. Respiratory data showing ventilatory settings and corresponding arterial blood gas values during supine and prone ventilation are shown in Table 1; the

Table 1. Various parameters of patient and ventilator setting during mechanical ventilation in the supine and prone position

<table>
<thead>
<tr>
<th>Position</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8 Postextubation (4 hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vent. Mode</td>
<td>Supine</td>
<td>Supine</td>
<td>Prone</td>
<td>Supine</td>
<td>Prone</td>
<td>Supine</td>
<td>Prone</td>
<td>Supine</td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.7</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>PEEP (cmH₂O)</td>
<td>8</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>10</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>PIP</td>
<td>25</td>
<td>28</td>
<td>32</td>
<td>23</td>
<td>24</td>
<td>30</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>Insp %</td>
<td>50%</td>
<td>50%</td>
<td>65%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>PH</td>
<td>7.33</td>
<td>7.36</td>
<td>7.46</td>
<td>7.47</td>
<td>7.46</td>
<td>7.43</td>
<td>7.39</td>
<td>7.41</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>45.1</td>
<td>45.1</td>
<td>45.1</td>
<td>45.1</td>
<td>45.1</td>
<td>45.1</td>
<td>45.1</td>
<td>45.1</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>58.8</td>
<td>58.8</td>
<td>58.8</td>
<td>58.8</td>
<td>58.8</td>
<td>58.8</td>
<td>58.8</td>
<td>58.8</td>
</tr>
<tr>
<td>BE</td>
<td>-2.4</td>
<td>-3.8</td>
<td>5.4</td>
<td>7.7</td>
<td>9.7</td>
<td>6.4</td>
<td>6.0</td>
<td>4.2</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>94</td>
<td>90</td>
<td>99</td>
<td>86</td>
<td>99</td>
<td>95</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>84</td>
<td>57.8</td>
<td>499.4</td>
<td>81.16</td>
<td>324.3</td>
<td>104.1</td>
<td>332.8</td>
<td>135.6</td>
</tr>
<tr>
<td>Qva/Qt (%)</td>
<td>36.0</td>
<td>43.6</td>
<td>7.2</td>
<td>46.7</td>
<td>12.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VC: volume-controlled ventilation; PC: pressure-controlled ventilation; FiO₂: inspired fraction of oxygen; PEEP: positive end-expiratory pressure; PIP: airway pressure; Insp %: percentage of the inspiratory cycle of ventilation; PaCO₂: arterial carbon dioxide tension; PaO₂: arterial oxygen tension; BE: base excess; SaO₂: arterial oxygen saturation; PaO₂/FiO₂: oxygenation index; Qva/Qt(%): shunt fraction
single best arterial blood gas reading during each event is shown.

Discussion
Acute respiratory failure is a rare but serious complication after cardiac surgery. Oxygenation and carbon dioxide elimination may be severely disturbed despite supplemental inspired oxygen and ventilation with increased tidal volume and respiratory frequency. The impairment of gas exchange is most likely multifactorial including the effects of sternotomy, ventilation perfusion inhomogeneity during mechanical ventilation and an impaired pulmonary capillary endothelium secondary to the release of biologically active substances during extracorporeal circulation (ECC). In addition, the effects of anesthesia and muscle paralysis may contribute to gas exchange impairment.

Increased extravascular lung water content has been proposed as a major cause for the development of respiratory insufficiency after cardiac surgery. Some studies show that elevated extravascular lung water content is present only immediately after extracorporeal circulation and in the early postoperative period. This suggests that additional mechanisms play an important role in the development of respiratory insufficiency.

Acute respiratory failure after cardiac surgery may be associated with atelectasis in dependent lung regions, which can be confirmed by computerized tomographic scans of the thorax. Conventional ventilatory therapy with moderate PEEP may be insufficient for the recruitment of collapsed alveoli. Ventilation in the prone position rapidly improves oxygenation without significant alteration of the hemodynamic state. Nonetheless, it is a grossly under-used technique, most likely because of the difficulty in providing nursing and other care to patients in this position.

Prone positioning results in a more uniform distribution of pleural pressure gradients, resulting in greater ventilation of the dependent lung than in the supine position. The hypotheses offered to explain the improvement in oxygenation in the prone position include: (1) increased functional residual capacity, (2) change in regional diaphragmatic motion, (3) redistribution of perfusion, and (4) better clearance of secretions. Animal models of ventilation/perfusion distribution have suggested that gravity has far less influence on the distribution of perfusion in the prone position, and the distribution of blood flow to various regions of the lungs is relatively unaffected by the change from the supine to the prone position.

Another possible explanation for the improvement associated with ventilation in the prone position is improved lymphatic flow. Almost all animals in nature lie prone when they are recumbent. Hence, it is reasonable to assume that lung lymphatics are evolved to drain the lung best in this position. Although only minor complications could be attributed to the prone position, careful positioning and regular examination to avoid pressure bruises are recommended. This patient had edema of the eyelid, conjunctival edema and subconjunctival hemorrhage, which resolved without treatment.

Patients who are 20% above their ideal body weight are obese. When they are 100% above this weight they are said to be morbidly obese. Patients with severe obesity generally have hypoxemia with a widened alveolar–arterial oxygen gradient due to ventilation–perfusion mismatch. Alveolar collapse at the bases of the lungs contributes to this phenomenon. Reduction in the functional residual capacity in the supine position increases ventilation–perfusion mismatch. Obese patients are therefore more likely to develop atelectasis and other postoperative pulmonary complications especially after upper abdominal and cardiovascular surgery.

Brussel et al. studied ten patients with acute respiratory failure after CABG using conventional mechanical ventilation in the supine and prone positions. Thoracic computed tomography scans revealed crest-shaped bilateral densities in the dependent lung regions in all the patients. In the supine position, systemic and pulmonary pressures were within the normal range, but oxygenation was severely impaired. After 2–5 hours of ventilation in the prone position, hemodynamic parameters did not differ between the supine and prone positions, but ventilation in the prone position improved gas exchange significantly. This study concluded that mechanical ventilation in the prone position might effectively recruit collapsed lung tissue and improve oxygenation without major hemodynamic consequences.

In our case, after bronchoscopic suctioning, PEEP was increased gradually to 12.5 cm H₂O and pressure-controlled inverse ratio ventilation was tried later. All these did not improve the PaO₂ of the patient. Chest X-ray (PA view) was normal. Computed tomography scan of the chest could not be done. Each time the patient was ventilated in the prone position, oxygenation improved significantly although hemodynamic parameters did not change.

We conclude that ventilation in the prone position is an effective method for improving oxygenation in patients with acute postoperative respiratory failure not responding to different ventilatory strategies.
References

1. Albert RK. Turnabout may be more than fair play. Crit Care Med 2000; 2: 571–572
“Concertina” Effect during Angioplasty of Tortuous Right and Left Coronary Arteries and Importance of Using Over-the-Wire System: A Case Report

Pravin K Goel, Ajay Agarwal, Aditya Kapoor
Department of Cardiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow

A case wherein “Concertina” effect appeared during angioplasty of both right and left coronary arteries is described. Also, the advantages of using an over-the-wire system in such cases are stressed especially when extreme tortuosity and total occlusion are present together. (Indian Heart J 2001; 53: 87-90)

Key Words: Angioplasty, Stents, Coronary disease

“Concertina” or “accordion” effect is the appearance of artefactual or pseudolesions during the course of percutaneous transluminal coronary angioplasty (PTCA) in tortuous vessels. The mechanism generally suggested is the partial straightening of a tortuous coronary artery by the coronary guidewire that causes mechanical invagination of the coronary arterial wall at various sites. Those performing angioplasties must be familiar with the appearance and mechanisms thereof, as failure to do so may lead to inappropriate intervention with its attendant risks. We describe a case in which the “concertina” effect appeared during the course of balloon angioplasty of both the right and left coronary arteries (RCA and LCA). The advantages of using an over-the-wire (OTW) system in arriving at a correct diagnosis and its successful management are also highlighted.

Case Report

A 58-year-old diabetic male patient presented with effort angina of recent onset. Coronary angiogram revealed an extremely tortuous RCA with an initial shepherd’s crook curve and total occlusion in the mid portion, immediately after a second near-90° bend (Figs 1a and b). Faint retrograde filling of the RCA through collaterals revealed the distal vessel to be even more sinuous. The LCA was free of significant disease except for a localized tight stenosis in the proximal part of a tortuous Ramus type vessel. The left ventricular function was normal. The patient was taken up for balloon angioplasty of the RCA followed by that of the Ramus.

Balloon angioplasty procedure: The RCA was intubated using an 8 F AL 1 guiding catheter which gave good support. A 0.014" high torque guidewire was first used to cross the lesion pre-loaded in a 3.0×20 mm OTW balloon. The lesion, however, could be reached only with great difficulty and additional balloon support was required because of extreme tortuosity in the proximal vessel. At this point, the floppy wire failed to cross the lesion. The balloon was then left in place just proximal to the lesion and the wire was changed to a standard one. The standard wire was then able to negotiate the lesion, but passage beyond it was difficult because of extreme distal tortuosity. The balloon and wire were then pushed together so as to float across the next bend (Fig. 2) but the duo also could not go further. At this stage, the balloon was again left in place in the RCA distal to the lesion, and the wire was changed to 0.014" intermediate. When this also failed to negotiate the lesion, the balloon was left at the same location and the wire was changed to a standard one. The standard wire was then able to negotiate the lesion, but passage beyond it was difficult because of extreme distal tortuosity. The balloon and wire were then pushed together so as to float across the next bend (Fig. 2) but the duo also could not go further. At this stage, the balloon was again left in place in the RCA distal to the lesion, and the wire was changed to 0.014" extra support, which gave the added support needed at this time. It was finally possible to get a stable wire position in the distal RCA. The balloon was then pulled back to the site of the lesion and inflated to the minimum pressure needed to get rid of the waist, following which a sustained inflation at low pressure of nearly 4 atm was maintained for about two minutes. Post-balloon dilatation contrast injection showed a patent RCA but multiple lesions appeared in the distal RCA (Fig. 3). The patient neither complained of any chest pain nor were there any ECG changes on the monitor.
Administration of intracoronary nitroglycerin did not reverse these lesions. At this stage, it was difficult to ascertain whether these distal narrowings were true lesions or the result of the so-called “concertina” effect due to stiffness of the intracoronary wire. In this case, there was no opportunity of knowing the pre-procedure disease status of the distal RCA, which was a totally occluded vessel with poor filling from collateral circulation. However, an OTW system was in place, we advanced the balloon over the coronary wire well beyond the segment showing the multiple lesions and the guidewire was pulled back into the guiding catheter. This removed the wire effect without loss of access to the distal vessel, the OTW balloon already being in place far distal to the lesion. Repeat injection showed total resolution of all lesions except one about 3 cm beyond the original occluded site (Fig. 4). It was then realized that this was the only true lesion amongst all the new narrowings that had been noted after opening of the total occlusion and it was balloon-dilatated at low pressure. The result was assessed with a second pullback of the wire and the balloon advanced as before so as to maintain access without the wire effect. Once the result was thought to be satisfactory, a 3.5×25 mm Multi Link stent was deployed at the site of the original occlusion and the entire system was pulled back. The final angiographic picture without the wire and balloon showed an excellent result with a widely patent artery by the extra stiff wire. This was, however, confirmed by repeating the steps of balloon advancement and wire withdrawal performed in the RCA. A 3.5×15 mm Multi Link stent was deployed in the Ramus without further delay. The final outcome was excellent (Fig. 8). The patient was discharged after 24 hours and was asymptomatic at six months follow-up. The follow-up angiogram done six months later showed almost normal-looking vessels with no restenosis.

Discussion

The appearance of an unexpected flow-limiting narrowing during the course of coronary angioplasty is a cause for great concern and requires rapid recognition and appropriate management. Frequently recognized causes include spasm, dissection, thrombus or embolization. Appearance of pseudolesions, or the so-called “concertina” or “accordion” effect is not uncommon but a less frequently recognized cause for such an appearance. Initially described by Grewe et al.1 in an internal mammary graft during PTCA of the native LAD, it has subsequently been described in several sporadic reports.2–10 There is a recent report of this occurring in a peripheral vessel during angiography.11 Most case reports describe this appearance during RCA angioplasty; the overall incidence is about 0.4 per cent. To the best of our knowledge, there have been no reports describing the effect in both the RCA and LCA in the same patient.

Mechanism: The basic mechanism for the appearance of these pseudolesions is the straightening of a tortuous coronary artery along its luminal axis by relatively stiff intracoronary equipment, usually the guidewire, running down its length.2–7,9 As the total length of the vessel has to remain constant, unless the wire system is flexible enough to take the turns and bends in the artery, the excess vessel tissue heeps up or invaginates along its length leading to the appearance of luminal encroachment, or at times, even a circulatory delay.

Management: Although it was initially reported that intracoronary nitroglycerin may “disinvaginate” the coronary wall,5 it is now well known that nitroglycerin is ineffective in relieving these lesions, thus effectively distinguishing them from a true spasm of the artery. It is vital to recognize the possibility of this “concertina” or “accordion” effect, because the mistaken diagnosis of a true new lesion by an unsuspecting operator may call for unwarranted repeat dilatations, turning a fully reversible phenomenon into a true iatrogenic complication.

The recommended routine for these cases has been the removal of all intracoronary material (including the guidewire and the balloon) into the guiding catheter to facilitate the vessel to reconform to its normal curvature with consequent disappearance of the pseudolesions.3 However, the problem with this approach is that if there were a true dissection, recrossing may be difficult and often
not free from the hazard of creating another dissection in these tortuous vessels with all its attendant risks. Chalet et al. proposed that the guidewire could be cautiously withdrawn up to a point where the floppy segment lies equally on either side of the pseudolesion, allowing the vessel to reconform to its normal shape and still retain contact with the distal tip of the wire lying beyond the lesion.
Our technique, however, goes a step further. Firstly, it involves no unprotected wire withdrawal, i.e. wire withdrawal without the balloon already in place in the distal vessel and this is possible only with an OTW system. This is of help to interventionists especially because it avoids the not so uncommonly encountered difficulty experienced by most interventionists in re-negotiating a tortuous vessel at times, in spite of reaching beyond the main lesion with the tip of the wire. Secondly, often the pseudolesions or the "concertina" effect may appear along a long segment of the vessel, as in our case, wherein withdrawing the guidewire partially (so as to leave only the floppy tip across that site) may not suffice. Thirdly, the risk of withdrawing the guidewire too far back always exists in a monorail system if one tries the technique of balloon advancement and wire pull-back.

The other major advantage of an OTW system in such cases is the ease of wire exchange. As described by us, this is not infrequently called for and then there is no need to repeat the initial steps in wire passage, with the balloon in place acting as a guide. Also, often it is these initial steps of vessel selection and wire passage that may be the most difficult in the case of extreme tortuosities and would not only call for extra time but could also damage the vessel at any point.

Conclusions: It is important for interventionists to be aware of the reversible "concertina" or "accordion" effect seen during angioplasty of extremely tortuous vessels. This would help in avoiding inappropriate dilatations due to a mistaken diagnosis of coronary dissection. We recommend the elective use of an OTW system while dealing with tortuous anatomy, especially with total occlusion added when distal vessel disease status is not known. Also, advancement of the balloon catheter over the guidewire into the distal vessel well beyond the site of the "concertina" effect followed by removal of the guidewire from the artery leads to complete resolution of this phenomenon.

References
7. Doshi S, Shiu MF. Coronary Pseudolesions induced in the left anterior descending and right coronary artery by the angioplasty guidewire. Int J Cardiol 1999; 68: 337-342
Hemangioma of the Pericardium: A Case Report

I Sathyamurthy, K Jayanthi, Rajan Santhosham
Department of Cardiology, Apollo Hospitals, Chennai

A 52-year-old male presented with dyspnoea on exertion. He was found to have a clinically normal cardiac status and a mass lesion in the anterior mediastinum, probably arising from the pericardium near the right atrium, as shown by both echocardiography and a computerized tomographic scan of the chest. He was successfully operated. The histopathology of the mass revealed it to be a hemangioma of the pericardium. This is one of the rare tumors of the pericardium and only a few cases have been reported in the literature. (Indian Heart J 2001; 53: 91–92)

Key Words: Hemangioma, Pericardium, Tumors

A number of primary and secondary neoplasms may involve the pericardium. Secondary neoplasia is much more common than primary tumors. 1 Mesothelioma is the most common primary pericardial neoplasm. We report a case of one of the rare primary benign neoplasms – hemangioma of the pericardium. The most common manifestation is pericardial effusion. Raised jugular venous pressure (JVP) and intrathoracic mass leads to a differential diagnosis of the superior vena cava (SVC) syndrome.

Case Report

A 52-year-old male presented with constant retrosternal chest discomfort of 10 years duration not associated with dyspnoea, palpitation, cough or giddiness. He was a hypertensive for nearly the same duration and was on β-blockers and angiotensin-converting enzyme (ACE) inhibitors. He had undergone a coronary angiography in 1997 which was reported as normal.

Clinically he was found to have normal heart sounds. JVP was not raised and BP was 100/70 mm Hg. There was no murmur, gallop or pericardial rub. Systemic examination did not reveal any abnormality. Electrocardiogram revealed sinus rhythm, normal QRS complexes and “T” inversion in the anterolateral leads. An X-ray chest PA view (Fig. 1) revealed a borderline increase in the cardiothoracic ratio (60%) and normal lung fields.

A two-dimensional transthoracic echocardiogram (Fig. 2) revealed normal cardiac chamber dimensions and contractility. The valves appeared to be normal. The left ventricular ejection fraction was 75%. There was no pericardial effusion. A circular solid mass measuring 5×4.5 cm was seen attached to the pericardium near the right atrium. This mass was not compressing any of the cardiac structures. It appeared to move with each cardiac cycle. A computerized tomographic (CT) scan of the chest done subsequently revealed a 5.9×5.5 cm noncontrast enhancing anterior mediastinal mass (Figs 3a and b).

The patient underwent surgical excision of the mass which was found to be attached to the epicardium over the right ventricle (RV) and extended to the RV outflow tract (Fig. 4). There were multiple feeders from the myocardial vessels to the mass. Histopathological examination of the excised mass revealed it to be a hemangioma (Figs 5a and b).
Discussion

Tumors of the heart, though uncommon, are potentially fatal. Sometimes they can be entirely removed by surgery with complete recovery. Prognosis is related to histological features, localization, rapidity of growth, and early diagnosis. Case reports of hemangioma of the pericardium describe surgical excision as the treatment of choice and complete recovery has been the rule. A case of a voluminous angioma adherent to the pulmonary artery and another of an epicardial hemangioma, have been previously reported. Patients with cavernous hemangioma located over the RV free well and extending to the RV outflow tract, similar to the present case, have been reported from Japan. Our patient also underwent successful surgical excision. The postoperative period was uneventful and a repeat echocardiogram did not show any mass.

References

Batista Procedure as a Bridge to Cardiac Transplantation

N Madhu Sankar, AR Baruah, Benjamin Ninan, S Rajan, KM Cherian
Institute of Cardiovascular Diseases, Chennai

End-stage heart failure is a major cause of morbidity and mortality among patients with severe dilated cardiomyopathy. Partial left ventriculectomy, introduced by Randas Batista, is being increasingly performed to treat these patients. Resection of a portion of the left ventricle with consequent reduction in left ventricular cavity leads to improvement in the function of the left ventricle. Clinical reports from various centers have shown improvement in heart failure symptoms after this procedure. However, consequent to redilatation, heart failure tends to progress in the follow-up period which makes the Batista procedure more suitable as an interim measure, i.e. a biological bridge to cardiac transplantation. We describe a case of severe dilated cardiomyopathy with end-stage heart failure. The patient underwent Batista procedure and, subsequently, cardiac transplantation.

Case Report

A 37-year-old male patient with worsening breathlessness due to dilated cardiomyopathy in the preceding 3 years was admitted in our institute for evaluation and management. Clinically, he had moderate mitral and tricuspid regurgitation which was confirmed by two-dimensional echocardiography. His coronary angiogram revealed ectatic coronary arteries with no flow-limiting lesion. Radionuclide scan showed severe left ventricular dysfunction with an ejection fraction of 11%. The left ventricular internal systolic diameter was 63 mm and the diastolic diameter was 70 mm. He was on maximal medical therapy which failed to improve his symptomatic status and he was put on the cardiac transplant waiting list. His condition deteriorated and he needed elective ventilation and inotropic support to evade impending cardiac arrest. Considering his severe symptomatic status and the nonavailability of a donor heart for transplant, we decided to perform the Batista procedure for symptomatic relief. He underwent partial left ventriculectomy by excision of the left ventricular wall between the two papillary muscles. The first obtuse marginal branch of the left circumflex artery was sacrificed in the resection, leaving the diagonals and the last obtuse marginal branch intact. The ventriculotomy was closed in two layers with pericardial buttressing suture. A posterior annular plication with pericardial buttressing was done for the mitral valve while a modified DeVega's annuloplasty was performed for the tricuspid valve. The postoperative course was uneventful and the patient was discharged on postoperative day 10. Two-dimensional echocardiography at the time of discharge revealed a left ventricular ejection fraction of 22% with trivial mitral and tricuspid regurgitation.

He was followed-up regularly and showed substantial symptomatic improvement during the first three months. Then his symptomatic status deteriorated gradually and the ejection fraction decreased to 17% without any increase in the severity of mitral or tricuspid regurgitation. The patient being young and severely symptomatic, cardiac transplantation was the only option available and he was put on the transplant list again. With a suitable donor heart being available, he underwent orthotopic heart transplantation. Recipient cardiectomy was extremely difficult due to the recent Batista procedure as the heart was densely adherent to the pericardium. Longer operative time was required with excessive bleeding and the heart was so adherent that a portion of the ventricular muscle had to
be left behind. He was shifted to the intensive care unit with inotropic support. He continued to bleed in the postoperative period leading to hemodynamic instability. Over the next seven days, he remained in low output failure and then succumbed to low cardiac output and multiple organ failure.

**Discussion**

The Batista procedure offers a new hope for patients with dilated cardiomyopathy and end-stage heart failure. Filho et al. have described their experience with the Batista procedure in 15 patients and concluded that this procedure improved the quality of life in the majority of patients and acted as a bridge to cardiac transplantation when donors are not available. McCarthy and Sabik from Cleveland Foundation have reported their experience with 53 patients: 1.9% perioperative mortality, 15% required left ventricular assist-device support, and 72% did not require re-listing for heart transplant. Based on their experience with ventricular remodelling surgery, Starling et al. have concluded that this procedure may delay or supplant the need for heart transplantation in selected patients. Takeshita et al. have performed angiographic-hemodynamic studies in 24 patients who underwent the Batista operation and suggested that it reverses heart failure by reducing both systolic and diastolic LV volume in selected patients immediately after surgery.

Cardiac transplantation has evolved to become a highly effective therapy in patients with dilated cardiomyopathy and end-stage heart failure. Lack of sufficient donors and socio-economic constraints associated with heart transplant still remain a challenge. In this scenario, left ventricular assist-devices may serve as a bridge to transplant, as an alternative to transplant or as a bridge to recovery. These bridging devices rearrange patient priority for transplantation and provide a reasonable quality of life for extended periods. Despite the fact that the patient died after cardiac transplant, we conclude that the Batista procedure may serve as a cost-effective biological bridge to transplant in patients with dilated cardiomyopathy and end-stage heart failure.

**References**

Aortic Valve Balloon Dilatation in a Newborn for Critical Aortic Stenosis Diagnosed During Fetal Life

A Saxena, N Naik, R Juneja
Department of Cardiology, All India Institute of Medical Sciences, New Delhi

Fetal echocardiography has enhanced the diagnostic armamentarium of congenital heart disease (CHD). It has permitted accurate prenatal assessment of cardiac anatomy and functional significance of various lesions. It has also made an impact, although modest, in prenatal therapy. Due to various technical limitations, interventions in fetal life have not been very successful. However, fetal echocardiography, in combination with an appropriately guided postnatal approach, can be used effectively in treating severe forms of CHD. We report a case in which diagnosis of a critical lesion during fetal life helped in planning treatment in the neonatal period.

Case Report

A 21-year-old primigravida was incidentally diagnosed to have a fetus with critical aortic stenosis (AS) at 30 weeks’ gestation. A decision to follow-up the fetus till term was taken as there was no evidence of congestive heart failure. Post-natal retrograde aortic valve balloon dilatation was performed 36 hours after birth. There was marked improvement in left ventricular function and the baby is doing well at 1-year follow-up. The need for accurate assessment of intracardiac anatomy during fetal life in critical aortic stenosis and its impact on therapeutic interventions is highlighted. (Indian Heart J 2001; 53: 95–96)

Key Words: Stenosis, Balloon, Valvuloplasty

and although the gradient was only 20 mmHg across the aortic valve, it was considered significant due to associated severe left ventricular dilatation and dysfunction with an estimated ejection fraction of only 15%–20%. At 24 hours after birth, the baby developed hypotension with poor peripheral perfusion and was put on prostaglandin E1 to keep the ductus arteriosus open, thereby maintaining the systemic circulation. Aortic valve balloon dilatation was done 36 hours after birth by the retrograde transfemoral route using a 5 mm balloon (Figs 1 and 2). The transaortic gradient, which was only 10–15 mmHg prior to balloon dilatation, was totally abolished. There was no aortic regurgitation following balloon dilatation on the aortic root angiogram (Fig. 2). The lower limb pulses on the side of catheterization returned 6 hours after the procedure following one dose of intravenous heparin. The baby continued to require inotropic support and prostaglandin E1 infusion for two more days to maintain the blood pressure and peripheral perfusion after which this support was weaned off. Hem made a gradual recovery and was discharged from the hospital after 10 days and placed on decongestive therapy and angiotensin converting enzyme inhibitors. The left ventricular ejection fraction at the time of discharge was 35% and the gradient across the aortic valve was 8 mmHg. The infant is now on follow-up for 13 months and the last echo-Doppler showed a left ventricular ejection fraction of 47% with a transaortic gradient of 6–8 mmHg.

Discussion

Critical AS in the neonate represents the favorable end of the spectrum of hypoplastic left heart syndrome. Patients
with aortic atresia, mitral atresia and hypoplastic left ventricle have a poorer prognosis with extremely high mortality rates and widely divergent therapeutic options. These patients are either chosen for single ventricle repair (Stage 1 Norwood or Fontan) or cardiac transplantation. Those with isolated critical AS without hypoplastic left ventricle represent a select group in whom the clinical outcome can be favorably altered. Deterioration in these infants, however, can be extremely rapid once the ductus arteriosus starts closing as their systemic blood flow cannot be maintained then. Therapeutic intervention is required immediately in the neonatal period in those with ductusdependent systemic circulation. These neonates require intensive care with correction of metabolic acidosis resulting from low cardiac output and prostaglandin E\textsubscript{1} to maintain ductal patency.\textsuperscript{3}

Transvenous balloon dilatation has been shown to be as efficacious as surgical treatment in terms of appearance of aortic regurgitation and relief of transvalvular gradient. Moreover, the early and mid-term results after neonatal aortic valve balloon dilatation have been shown to be good, with survival rates better than those of the surgical series.\textsuperscript{4} Both the retrograde and antegrade routes have been employed, though the latter method is technically more demanding.\textsuperscript{5} Besides the femoral artery, the umbilical artery, transcarotid approach and subscapular artery cutdown have been used for retrograde approach to the valve. Loss of the femoral artery pulse is a common complication after this procedure which is now seen less frequently with the use of low-profile catheters.

The need for an accurate assessment of cardiac anatomy in the fetus with aortic stenosis cannot be overemphasized. Therapeutic options and their timing are guided by fetal echocardiography. Fetuses with a small fossa ovalis, endocardial fibroelastosis, poor left ventricular function, other obstructive lesions on the the left side and right ventricular dysfunction have a poor prognosis. Absence of growth of the left ventricle on serial echocardiographic examination also carries a poor prognosis.\textsuperscript{6} It is imperative to differentiate aortic stenosis from a primary cardiomyopathy of the left ventricle. The presence of a normal aortic valve with no Doppler gradient across it and the absence of post-stenotic dilatation go against critical aortic stenosis. In addition, it should be recognized that the peak gradient alone does not reflect the severity of obstruction across a valve. Severe left ventricular dysfunction and prostaglandin E\textsubscript{1} may markedly reduce gradient across the aortic valve in critical AS. In this situation, the width of the stenotic jet may help in assessing the true significance of valvular stenosis.

In conclusion, the diagnosis of a critical cardiac lesion during fetal life by echocardiography helps in the optimal management of the baby. At the appropriate time, the mother can be transferred to a center suitably equipped for managing these newborns.

References
A 21-year-old male presented with episodes of paroxysmal tachycardia mediated via a concealed posteroseptal accessory pathway. He was also found to have a diverticulum of the coronary sinus. However, successful radiofrequency ablation was achieved only endocardially under the mitral annulus and not within the diverticulum. (Indian Heart J 2001; 53: 97-99)

Key Words: Radiofrequency ablation, Tachyarrhythmias, Conduction

Coronary sinus (CS) anomalies such as diverticulum, enlarged CS ostia and persistent left superior vena cava (SVC) are found in 9% of patients with supra-ventricular tachycardia. Diverticulum of the proximal CS is found in 7% of patients with manifest accessory pathways (APs), but have not been reported in those with concealed APs. In patients with overt posteroseptal APs and CS diverticula, the successful ablation site has always been found to be epicardial, within the CS diverticulum, usually in the neck. We report a unique case of concealed left posteroseptal AP and diverticulum of the CS in which successful radiofrequency (RF) ablation could be achieved only endocardially.

Case Report

A 21-year-old man presented with three episodes of paroxysmal palpitations associated with presyncope requiring hospitalization. Adenosine successfully terminated the narrow QRS tachycardia. The sinus rhythm ECG was normal with no suggestion of pre-excitation. Clinical examination, chest X-ray and echocardiography were normal. He underwent electrophysiological study (EPS) with a view to identify the mechanism of tachycardia and for RF ablation.

EPS was performed using an EMS computerized system (CARIM, Maastricht, The Netherlands). A deflectable decapolar (Cordis–Webster) catheter was placed in the coronary sinus, a quadripolar (Josephson curve) catheter was placed in the His bundle region and right ventricle.

Ventricular extra stimuli reproducibly induced orthodromic atrioventricular re-entrant tachycardia using the left posteroseptal AP in a retrograde direction. A 4 mm distal tip quadripolar (Cordis–Webster) thermocouplesmall-curve catheter was used for mapping. The earliest atrial activation during ventricular pacing and orthodromic tachycardia along the mitral annulus did not reveal early activation. At this stage, a left coronary arteriogram was performed which revealed a CS diverticulum, appreciated in the venous phase. The CS angiogram confirmed a wide-mouthed, globular diverticulum (Figs 1a and b). The mapping was performed during orthodromic tachycardia. Mapping inside the diverticulum showed the earliest atrial activation to be later than the earliest activation in the decapolar catheter placed in the coronary sinus (Fig. 2). Attempts at RF ablation along the neck and body of the diverticulum were unsuccessful.
Coronary Sinus Diverticulum

Fig. 1b. Coronary sinus angiogram in 30° RAO view, showing coronary sinus diverticulum (arrow).

Fig. 2. Recording from inside the diverticulum (RFd) during orthodromic tachycardia. The decapolar catheter was partly outside the coronary sinus as seen in Figure 1a; CS56 electrodes are situated at the coronary sinus ostium. The earliest atrial activation is seen in CS34, which is just within the coronary sinus. The atrial activation in the mapping catheter (RFd) is later than that in CS34.

Fig. 3a. Site of RF ablation in 45° LAO view, showing the position of the ablation catheter (arrow).

Retrograde transaortic mapping was repeated and the earliest activation was seen adjacent to the distal end of the diverticulum (Figs 3a and b). At this site, there was a clear pathway potential which preceded the earliest atrial activation in the decapolar catheter (Fig. 4). Successful RF ablation of the left posteroseptal pathway was performed at this endocardial site; the tachycardia terminated within 5 seconds of starting the RF energy. Ventriculo-atrial (VA) dissociation was seen after the RF ablation. After ablation, a vigorous stimulation protocol, with isoprenaline as well, failed to induce tachycardia.

Discussion

While enlargement of the CS ostium has been reported in 5% of patients with atrioventricular nodal re-entrant
tachycardia (AVNRT), diverticulum of the proximal CS is associated with manifest posteroseptal APs. These APs are difficult to ablate endocardially outside the diverticulum and successful ablation is often performed from within the diverticulum. Thus CS angiography is suggested prior to catheter ablation of posteroseptal APs, especially when endocardial signals are not optimal.4

Our patient was unique, with a CS diverticulum and concealed AP as opposed to manifest pre-excitation. Also, the site of successful ablation was endocardial, under the mitral annulus, and not within the diverticulum. Thus the CS diverticulum, as a misleading "red herring", was a purely incidental finding in our patient.

References

Fatal Atypical Mycobacterial Infection in a Cardiac Transplant Recipient

Ruma Ray, Soumitesh Chakravorty, Jaya S Tyagi, B Airan, KK Talwar, P Venugopal, P Chopra
Departments of Pathology, Biotechnology, Cardiology and Cardiothoracic Surgery, All India Institute of Medical Sciences, New Delhi

Giant cell myocarditis (GCM) is a rare and frequently fatal disorder of unknown origin that is defined histopathologically as diffuse myocardial necrosis with multinucleated giant cells in the absence of sarcoid-like granulomas.¹,² Cardiac transplantation is the treatment of choice though the disease is known to recur in the donor heart.² Occurrence of atypical mycobacterial infection in a cardiac transplant recipient is rare. We present a fatal case of atypical mycobacterial infection in a cardiac transplant recipient who underwent heart transplantation for GCM.

Case Report

This 37-year-old female was clinically diagnosed as dilated cardiomyopathy. Pre-transplant endomyocardial biopsy revealed non specific features, e.g. mild focal thickening of the endocardium, myocyte hypertrophy with nucleomegaly and sarcoplasmic degenerative changes. There was no myocarditis in the material examined. The patient underwent orthotopic cardiac transplantation for intractable cardiac failure. In the postoperative period, the patient was on immunosuppressive therapy with cyclosporin, azathioprine and prednisolone. Four endomyocardial biopsies were taken on days 10, 20, 30 and 60 following transplantation. The first two biopsies revealed acute rejection of grade IA (ISHLT). The third biopsy showed focal ischemic changes while the fourth one showed interstitial fibrosis and myocyte hypertrophy. The patient expired on day 100 following transplantation. Postmortem biopsies from the heart and left lung were taken for pathological examination.

Pathology:
The native heart: The heart weighed 235 g. Due to the operative technique, parts of both the atria and outflow tracts of the ventricles were not included in the specimen. On external examination, the pericardial surface showed a few small 0.1–0.2 cm grey-whitened necrotic areas. On opening the heart, part of the right atrium included in the specimen and the tricuspid valve were normal. The right ventricular cavity had focal endocardial thickening which was especially prominent over the septal wall. The inflow tract of the right ventricle just beneath the tricuspid valve had a...
thrombus, 0.5 cm in diameter. The left atrium and the mitral valve were normal. The left ventricular cavity was dilated and showed diffuse endocardial thickening. The ventricular myocardium had multiple small grey-white areas 0.1–0.2 cm in diameter. Segments of the epicardial coronary arteries included in the specimen were normal.

On light microscopic examination, multiple sections from all the chambers showed large areas of myonecrosis and lymphohistiocytic infiltrate with numerous giant cells (Fig. 1). There was endocardial thickening, widespread myocyte degeneration and focal replacement fibrosis. No definite epithelioid cell granuloma was noted. Periodic acid Schiff and silver methenamine stains for fungus did not demonstrate any fungal profile. Ziehl–Neelsen and auramine–rhodamine stains for acid-fast bacilli were negative. The coronary arteries were histologically normal. In view of the presence of numerous giant cells with myonecrosis in the absence of distinct sarcoid-like granulomas, the diagnosis of giant cell myocarditis was considered.

Postmortem biopsy specimens: Postmortem biopsy samples included tissues from the donor heart and the left lung of the patient. On light microscopic evaluation, the endocardium was normal. The myocardium revealed non-specific changes like myofibre hypertrophy and focal interstitial edema. The pericardium had multiple discrete necrotizing granulomas showing central necrosis with a few epithelioid and giant cells. Sections from the lung showed similar epithelioid cell granulomas (Fig. 2). Ziehl–Neelsen stain for acid-fast bacilli demonstrated numerous acid-fast Mycobacterium tuberculosis-like organisms both in the pericardial and pulmonary granulomas. No fungal profile or inclusion of cytomegalovirus infection was identified in the specimen examined. A diagnosis of tuberculosis involving the pericardium and lung was suggested. Subsequently samples from the explanted native heart (on which the diagnosis of GCM was earlier made) and postmortem biopsies from the heart and lung (histologically diagnosed as tubercular) were subjected to polymerase chain reaction (PCR) analysis for the detection of Mycobacteria in general and M. tuberculosis in particular.

**Polymerase chain reaction:**

Analysis of the native heart and postmortem samples: Samples for PCR were retrieved in the form of scrapings of paraffin-embedded tissue from paraffin blocks and transferred to 1.5 ml polypropylene tubes (Axygen Inc.). The samples were deparaffinized by extraction with xylene. Residual xylene was removed by extraction with 100% ethanol, tissue pellets were dried using acetone and DNA was extracted using 10% Chelex 100. Polymerase chain reaction was performed with the supernatant as follows:

1. 23 S rDNA PCR assay specific for genus Mycobacterium was done. An amplification product of 174 bps was seen as expected in the postmortem lung (Fig. 3a) and donor

**Fig. 3a.** Amplification of mycobacterial DNA from paraffin-embedded lung tissue. Amplification reaction products were electrophoresed and visualized by ethidium bromide staining. Lane M, molecular weight marker; lanes 1 and 2, DNA from postmortem lung tissue (undiluted and 1:10 dilution, respectively); lane 3, DNA-negative control; lane 4, M. tuberculosis DNA-positive control; lane 5, M. tuberculosis DNA-negative control; lanes 6 and 7, DNA-negative control.

**Fig. 3b.** Amplification of mycobacterial DNA from paraffin-embedded heart tissue. Amplification reaction products were electrophoresed and visualized by ethidium bromide staining. Lane M, molecular weight marker; lane 1, DNA isolated from implanted donor heart tissue (postmortem); lane 2, DNA isolated from explanted native heart; lane 3, M. tuberculosis DNA-positive control; lane 4, DNA-negative control; lane 5, DNA isolated from implanted donor heart; lane 6, M. tuberculosis DNA-positive control; lane 7, DNA-negative control.
heart (Fig. 3b) samples, indicating the presence of an organism belonging to the genus Mycobacterium. PCR failed to amplify 23S rDNA sequences from the explanted native heart (Fig. 3b) and thereby, the possibility of tuberculosis in the native heart could be ruled out.

(2) DevR-based PCR assay was not performed in the explanted heart tissue as the 23S rDNA-based genus-specific PCR assay failed to amplify mycobacterial DNA (Fig. 3b). Following step 1, devR-based PCR was performed in the postmortem samples from the lung and donor heart. This assay generates a 513 bps DNA product specific for M. tuberculosis which was negative in these samples (Figs 3a and 3b). The positivity of 23S rDNA assay and a negative M. tuberculosis complex-specific assay suggested the presence of nontubercular Mycobacterium (atypical Mycobacterium) in the postmortem samples of the heart and lung. The causative mycobacterial species could not be identified further due to the nonavailability of species-specific PCR for assays of nontubercular Mycobacterium in our PCR laboratory.

Discussion

Cardiac transplantation is an accepted therapeutic modality in patients with intractable heart disease. GCM is a rare disorder characterized histologically by the presence of diffuse inflammatory infiltrates with multinucleated giant cells in the absence of sarcoid-like granulomas. Cardiac transplantation is a recommended therapeutic procedure in this condition as the disease is otherwise fatal. Histological examination of the explanted native heart in the present case revealed myocardial necrosis with lymphohistiocytic infiltrate and giant cells. There was no obvious granulomatous reaction or presence of acid-fast bacilli and thus the diagnosis of GCM was made.

In the post-transplant period, the patient underwent episodes of acute rejection and finally succumbed to disseminated atypical mycobacterial infection involving the heart and lungs. While examining the pathological material from transplant recipients, the possibility of infection should always be considered as these patients are immunosuppressed. The two most common infections which can be identified and diagnosed on endomyocardial biopsy are cytomegalovirus infection and toxoplasmosis. Though tuberculosis has occasionally been described in cardiac transplant recipients, the occurrence of atypical mycobacterial infection in such patients is distinctly rare.

The incidence of tuberculosis among patients undergoing antirejection therapy is considerably higher than that in the general population and heart transplant recipients have been found to carry the highest risk of tuberculosis. Though infections due to nontubercular Mycobacterium in solid organ transplant recipients are infrequent, they may be a major cause of morbidity in such patients. The reported prevalence of disease in a heart transplantation program due to nontubercular Mycobacterium is 0.24%. In the disseminated form of the disease, the lungs and subcutaneous tissue are commonly involved. Intestinal involvement has rarely been reported in the literature. Our patient is unique as she had a fatal outcome due to atypical mycobacterial infection involving the lungs and heart within 100 days of transplantation. Other organs could not be examined as an autopsy was not conducted on the patient.

A high degree of clinical suspicion of tubercular infection is required in cardiac transplant recipients and the diagnosis needs to be confirmed by histological examination and/or cultures. Postmortem specimens from the heart and lung in the present case revealed multiple small necrotizing granulomas. Ziehl–Neelsen stain demonstrated numerous acid-fast bacilli and a provisional diagnosis of tuberculosis was offered. The final diagnosis of nontubercular mycobacterial infection could only be made following PCR analysis of tissues retrieved from the paraffin block as the genus-specific PCR product was amplified without amplification of M. tuberculosis DNA. Polymerase chain reaction has revolutionized the entire spectrum of molecular biology as it can offer rapid definitive diagnosis of an infective organism including its species specification and antibiotic resistance profile. Retrieval of tissue from paraffin-embedded material and subsequent PCR analysis can provide an accurate etiological diagnosis even when the culture report is not available to the pathologist, as in the present case. While examining the postmortem specimens, we had a re-look at the original diagnosis of GCM made on the explanted native heart. The possibility of undiagnosed mycobacterial infection with widespread necrosis and giant cell reaction could be ruled out due to the absence of granulomas, negative Ziehl–Neelsen and auramine-rhodamine staining and non-amplification of genus-specific PCR product on retrospective PCR analysis. Thus, heart transplantation should be considered an unheralded risk factor for mycobacterial infection, particularly in countries such as India where the disease is prevalent.

References


---

**Foundation of Cardiovascular Sciences**

**Award of Financial Assistance for Attending International Conferences/Travelling Abroad on Fellowships**

Applications are invited from medical scientists engaged in research in cardiovascular and allied sciences for grant of financial assistance to participate in international conferences/travelling abroad on fellowships.

The foundation shall provide partial financial grants to cover travel and registration fee for applicants whose papers have been accepted for presentation, or who have been invited to chair an important session. Cases would be decided on individual basis and the decision of the trustees would be final.

Applications with full bio-data, proof of acceptance of paper for presentation/invitation to chair a session, four copies of the abstract, and a copy of the brochure of the conference should be submitted at the following address at least eight weeks before the date of the conference.

For requests to participate in fellowship programmes, full details of the programme along with the letter of "grant of fellowship" should be submitted.

Managing Trustee
Foundation of Cardiovascular Sciences
3C, North West Avenue
Punjabi Bagh
New Delhi 110026
Identification and Stabilization of Vulnerable Atherosclerotic Plaques: The Role of Coronary Thermography and External Heat Delivery

Christodoulos Stefanadis, Konstantinos Toutouzas, Eleftherios Tsiamis, Christos Pitsavos, Lila Papadimitriou, Pavlos Toutouzas
University of Athens, Greece

The morphology and cellular component of atherosclerotic plaques, rather than the degree of stenosis, are considered to be the most important determinants for the formation of thrombus leading to acute coronary syndromes. The characteristics of the plaque provide significant information regarding the vulnerability and these may be obtained by several imaging methods. Recently, new techniques have been proposed for the identification of vulnerable plaques which may help in understanding the pathophysiological mechanisms implicated in the rupture of atherosclerotic coronary lesions.

Morphology of vulnerable atherosclerotic plaques:
At present, the atherosclerotic plaque is not considered only as a mass in the coronary artery which progressively increases and obstructs the lumen of the artery. The plaque contains active cells that play a significant role in its stability. The cellular component of the lesion leads to multiple pathophysiological pathways producing different clinical syndromes.

Clinically stable plaques have thick fibrous caps and small lipid cores with abundance of extracellular matrix. The lesions do not necessarily produce significant degrees of stenoses. In contrast, vulnerable plaques have thin fibrous caps separating the core from the arterial lumen and thus the risk for plaque rupture is increased. The fissure of an atherosclerotic plaque primarily occurs in eccentric lesions at the regions in which the fibrous cap is often thinnest and has a reduced collagen content. In these regions, a high circumferential stress develops and the risk for plaque rupture is substantially increased. Moreover, the thickness of the fibrous cap is inversely correlated with the circumferential stress. In addition, atherosclerotic plaques with large lipid cores occupying more than 40% of the plaque volume are at high risk for thrombosis. The consistency of the lipid core also plays an important role in the vulnerability of the plaque, since if the lipid core is soft the risk for plaque rupture is increased.

Progression of a Plaque: The role of inflammation:
A significant factor that leads to the progression of an atherosclerotic plaque from a stable to an unstable status is inflammation. Adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM) increase the concentration of leucocyte receptors on the endothelium. Thus, leucocytes intrude into the lesion and by absorbing lipids become macrophages. This process is primarily mediated by cytokines (tumor necrosis factor-α, interleukins, monocyte chemoattractant protein-1), which are proteins produced by inflammatory cells, such as mastocytes, macrophages and lymphocytes. The concentration of these inflammatory cells within the coronary atherosclerotic plaque correlates with the clinical syndrome. Accordingly, macrophages are more frequently demonstrated in coronary specimens obtained from patients suffering from unstable angina compared with patients with stable syndromes. In addition, lymphocytes are activated in patients with unstable angina as compared with patients with effort angina or control patients. Interleukin-2 receptors are also increased substantially in patients with unstable syndromes. These cellular components release growth factors by autocrine and paracrine control. Growth factors lead to the development of extracellular matrix, and hypertrophy and hyperplasia of smooth muscle cells. However, macrophages and other plaque-related cell types also release matrix degrading proteases, the matrix metalloproteases (MMPs). MMPs are pro-inflammatory substances and they initiate the degradation of fibrillar collagen leading to vulnerability of the atherosclerotic plaque. Indeed, Sukhova et al. demonstrated that concentrations of MMP-1 and MMP-13 were increased in vulnerable atheromatous plaques compared to stable fibrous plaques.

Thus, the progression of a stable lesion to a vulnerable atheromatous plaque is mediated by the development of lipids and the interactions of inflammatory cells. In contrast, stabilization of a plaque is mediated by an increase...
in the amount of extracellular matrix and smooth muscle cells. The major problem, however, is the detection of plaques that will become vulnerable and produce acute coronary syndromes.

Detection of vulnerable plaques: The aim of diagnostic procedures such as imaging techniques, is to provide information regarding the morphological characteristics of the atherosclerotic plaques, and also to assess the physiological pattern of the coronary plaques. Morphological characteristics are related to the anatomical changes of the coronary vessel wall (lumen diameter, lumen area, vessel area, remodeling index). For physiological assessment, measurements of coronary pressure, flow, temperature, and elasticity are required. Ideally, the morphological and physiological parameters should be obtained by noninvasive methods. Moreover, such methods could be used as a "screening" test and if necessary, therapeutic intervention could be initiated for the reduction of future adverse cardiac events. However, a method providing all this information is still not available and most imaging techniques are invasive. In addition, pharmacological or mechanical intervention based on the findings of coronary plaque characteristics has not yet been proved by clinical trials.

Intravascular ultrasound (IVUS) is a catheter-based technique that provides tomographic images of the arterial wall and morphometric data of lumen and vessel dimensions. Recent studies have shown that lipid-rich areas and the thickness of the fibrous cap may be visualized by high-frequency IVUS. However, more histological studies are required for the validation of these observations. Another significant information provided by IVUS is the remodeling of the vessel wall. Several reports demonstrate a correlation between positive remodeling and vulnerability of the plaque. This intriguing relation between remodeling and vulnerability needs to be further investigated. Elastography is an IVUS catheter-based technique for tissue characterization. In vitro studies have used validation of elastography to discriminate lipid-rich areas from fibrous plaques. The clinical application of this technique is awaited with great interest. In addition, angioscopy is a well described method that provides visualization of the plaque with high sensitivity. The inability to provide morphological characteristics of the plaque and the arterial wall layers negates the diagnostic ability of angioscopy. Several attempts have been made to improve the resolution of magnetic resonance imaging (MRI). Although in experimental studies the regression of atherosclerotic plaques has been documented by MRI, its clinical application provides information only for atheromatous plaques in large arteries such as the aorta and the carotids. Accordingly, intravascular MRI is currently under investigation to address the limitations of the noninvasive procedure. Furthermore, nuclear scintigraphy imaging techniques are being examined for the detection of vulnerable plaques. Lately, a new method has been introduced for the visualization of the arterial wall. Optical coherence tomography (OCT) represents a new imaging modality at a level of resolution not previously achieved by IVUS. OCT is a catheter-based technique utilizing back-reflected infrared light to obtain in situ micron-scale tomographic imaging. This method is attractive since it may differentiate lipid-based and water-based constituents even in heavily calcified tissue. The clinical application of this method is eagerly awaited. Only preliminary results are available for a new method for the identification of the necrotic core and vulnerable atherosclerotic plaque. This involves the detection of lysoecitin, one of the active components of oxidized low-density lipoprotein by laser-induced fluorescence. Near-infrared spectroscopy is being tested currently as a method for the detection of vulnerable plaques.

Coronary Thermography

It is known that most ruptured plaques are characterized by a large pool of cholesterol or necrotic debris and a thin fibrous cap with a dense infiltration of macrophages. Casscells et al. postulated that both types of thrombotic events may be predicted by the heat released by activated macrophages either on the plaque surface or under a thin cap. Thus, they measured the intimal surface temperatures of carotid artery plaques taken at endarterectomy. The living samples were probed with a thermistor (24-gauge needle-tip; accuracy 0.1°C; time contrast 0.15 s). The plaques had several regions in which surface temperatures varied by 0.2–0.3°C, but 37% of the plaques had substantially warmer regions (0.4–2.2°C). Moreover, the temperature correlated positively with cell density \( r=0.68, p=0.0001 \). The results of this fundamental study raised the possibility that a catheter which can localize heat or metabolic activity might be able to identify plaques at high risk of rupture or thrombosis. In order to measure the temperature of the atherosclerotic plaques in vivo, we proceeded to design and manufacture a "thermography" catheter to be able to apply this technique in clinical practice.

Thermography Catheter: For the measurement of temperature we use a thermistor probe (Microchip NTC Thermistor, model 100K6MCD368, Beta THERM). The
The diameter of this probe is minimal (0.457 mm) and therefore, it is appropriate for the human coronary arteries. The technical characteristics of the thermistor include: (i) temperature accuracy of 0.05 °C; (ii) time constant of 300 msec; (iii) spatial resolution of 0.5 mm; and (iv) linear correlation of resistance vs. temperature over the range of 33–43 °C.29–31 The thermistor probe is attached to the distal end of a long, 3 F shaft. The gold-plated lead wires of the thermistor pass through the shaft and end in a connector at the distal part of the thermography catheter. The catheter also has a lumen for the guidewire. The guidewire enters at the distal end of the catheter and it is extended 20 cm proximal to the end of the catheter. In order to ensure contact between the thermistor probe and the vessel wall, a hydrofoil is positioned opposite the thermistor. At the site of the hydrofoil and the thermistor the thickness of the catheter is 4 F.

For data acquisition and processing, in our early experience the thermistor leads were connected to a Wheatstone bridge (a type of null comparator), which is used to correlate the change of thermistor resistance (which varies with temperature) to voltage changes. Subsequently, voltage changes were fed into a personal computer with an analog-to-digital converter and displayed in real-time mode. Voltage changes were correlated with temperature values by using commercially available software (Dataflow, Crystal Biotech) after calibration at temperatures varying from 33 °C to 43 °C (balancing the Wheatstone bridge to 0.00 V at 33 °C).

Presently, the thermistor leads are connected to a digital multimeter (Protek 506) with an RS232C interface. The multimeter is connected to a personal computer (200 MHz Intel Pentium) and the resistance is displayed real-time. Resistance changes are correlated with temperature changes according to the Steinhart-Hart equation. This is a single equation that relates resistance and temperature of thermistors. Finally, after the conversion of resistance values to temperature values (by Microsoft Excel) the temperature changes are displayed on the screen of the personal computer. All data are stored in the computer.

**Thermal Heterogeneity in Human Coronary Arteries:**

After the successful experimental testing of the thermography catheter we proceeded to the clinical application. We perform quantitative coronary angiography in all patients and the minimal lumen diameter and reference diameter are measured by using the guiding catheter filled with contrast as a scaling factor. Moreover, an IVUS catheter is introduced into the target vessel for detailed mapping of the area of interest. Thereafter, balloon angioplasty is performed. Five minutes after a contrast injection, the thermography catheter is advanced through the guiding catheter, and blood temperature is measured when the thermistor just emerges from the tip of the guiding catheter without being in contact with the vessel wall. Thereafter, the temperature of the lesion is measured. In the preliminary studies we examined the heterogeneity of the atherosclerotic plaques by measuring the temperature of the plaque. Accordingly, the difference of temperature (ΔT) between the atherosclerotic plaque and the healthy vessel wall is calculated by subtracting the background temperature from the maximum temperature of the atherosclerotic plaque.

In the first clinical study, we examined the thermal heterogeneity of atherosclerotic plaques in patients with different clinical syndromes. Thus, we measured the thermal heterogeneity in patients with stable and unstable angina, and acute myocardial infarction. The temperature of the healthy vessel wall was constant and varied by only 0.05 °C (SD 0–0.026). The majority of atherosclerotic plaques showed higher surface temperatures compared to the normal vessel wall. Moreover, the differences in temperature were not correlated with the degree of stenosis. Heterogeneity within the atherosclerotic plaques was shown in 20%, 40%, and 67% of the patients with stable angina, unstable angina, and acute myocardial infarction, respectively, whereas no heterogeneity was shown in the control subjects. Greater values of ΔT were observed in patients with unstable angina (maximum, 1.55 °C) and acute myocardial infarction (maximum, 2.60 °C). ΔT was different among the groups, increasing progressively from patients with stable angina to those with acute myocardial infarction. Multiple regression analysis revealed that C-reactive protein was the only factor significantly associated with ΔT.

The first study showing thermal heterogeneity ex vivo within atherosclerotic plaques by Casscells et al.28 also demonstrated a relationship between the number of infiltrated macrophages and thermal heterogeneity. A recent study by our group demonstrated that increased plaque temperature in vivo is associated with acute phase reactants, and that the increased temperature indicates an aggressive inflammation.30 Accordingly, it seems that inflammation plays a significant role in heat release from atherosclerotic plaques. Previous studies showed that an inflammatory process is involved at the onset of acute coronary syndromes and is also present in culprit lesions of patients with effort angina.32

The considerable overlap of plaque temperature in patients with effort angina and those with acute coronary syndromes leads to the hypothesis that the process leading to increased temperature precedes plaque rupture.
Moreover, a percentage of patients with clinically stable angina have unstable plaques. Previous studies have shown that the concentration of C-reactive protein is associated with coronary events in patients with stable or unstable angina. In addition, a significant percentage of lesions in patients with stable angina contain intercellular calcium channels that are associated with calcium. The ARMS study (Angina Risk in Men Study) demonstrated that inflammatory activity is involved in disease progression in stable angina. However, fibroblast and white blood cell counts were independent predictors of cardiovascular death or nonfatal myocardial infarction in this group of patients. Also, patients with stable angina pectoris who developed myocardial infarction or died of cardiovascular causes had elevated serum levels of soluble cell adhesion molecules indicating increased inflammatory activity. Furthermore, histologically stable atherosclerotic plaques are not associated with the presence of clinically stable angina, since a considerable overlap in inflammatory activity in plaque tissues is observed within the clinical syndromes.

Clinical application of thermography: In a recent study we evaluated the clinical significance of temperature measurement of atherosclerotic plaques for clinical outcome following percutaneous coronary intervention. All patients enrolled in this study had one-vessel disease and were suffering from stable or unstable angina, or acute myocardial infarction. Accordingly, in 86 patients \( \Delta T \) was measured and they were then followed up clinically for approximately 2 years. During the follow-up period, 21 patients had an adverse cardiac event. \( \Delta T \) was greater in patients with adverse cardiac events compared to patients without events (\( \Delta T: 0.939 \pm 0.49 \text{ v. } 0.428 \pm 0.42, p < 0.0001 \)). Moreover, in each group, \( \Delta T \) was greater in patients with adverse cardiac events, although in patients with acute myocardial infarction this difference did not reach statistical significance. The application of Cox regression analysis revealed that \( \Delta T \) was a strong predictor for adverse cardiac events during the follow-up period (odds ratio 1.92, \( p = 0.008 \)). Moreover, patients with \( \Delta T \geq 0.5 \) °C had an almost 6 times (41% v. 7%) increased risk for an adverse cardiac event compared to patients without increased \( \Delta T \).

The inflammation of lesions in patients with inflammatory cells during percutaneous intervention may indicate those lesions that are predisposed to future alterations of plaque morphology. Moreover, macrophages and T-lymphocytes are present in the majority of restenotic lesions of patients presenting with unstable angina and this inflammatory reaction is related to the underlying morphology. On the contrary, the smooth muscle cell area is similar in restenotic lesions of patients with stable or unstable angina.

External heat delivery: It is known that thermotherapy is currently applied in several proliferative diseases. Heat is a physical agent whose biological effects depend on the intensity, duration and means of application. Different heat applications have been used, varying from laser devices to high-intensity focused ultrasound and radiofrequency. Most of these methods are applied invasively. Hyperthermia is emerging as an effective treatment in proliferative conditions such as benign prostatic hyperplasia, brain tumors and bone tumors. The goal of heating is to destroy tissue by achieving temperatures that exceed the cytotoxic threshold and induce cell death. The threshold depends on the cell type and thus when heterogeneous tissue is treated, only a percentage of cells within the treated area will die.

In our center during the past few years, we performed experimental studies in which magnetic energy was used to heat noninvasively stented arterial segments from a distance. This type of energy creates an alternating magnetic field that exclusively targets metals such as stents. An alternating magnetic field from an induction heating furnace has also been applied by other investigators for heating stents or bone cement. By this noninvasive method, stents are heated externally from a distance and the heat is transmitted by conduction in the stented arterial wall in a controlled mode.

We used a high-power generator for the production of electromagnetic energy (18 kW). The voltage and the current drain were controlled by a software that was designed in our institute. This energy was driven to a specially designed inductor in order to create a periodically alternating magnetic field (20 MHz). Thus, a magnetic force was produced which changed with the same frequency as the magnetic field. As the magnetic force changed periodically on the stent, energy was drained from the generator to compensate for the lagging of the magnetic flux. Accordingly, the magnetic force appears on the metallic target as heat. This type of energy heats only metals such as stents from a distance. By regulating the generator's output power, the magnetic force produced is completely controlled.

In vivo experimental studies in porcine coronary arteries were performed by applying magnetic force until the temperature of the stent reached 43 °C. We implanted stents in the left anterior descending artery in 15 animals and, after a heating session, stents were implanted in the left circumflex artery. Acute thrombosis was not observed in
any case. The in-stent luminal diameter at 4 weeks was similar in the heated and control segments (2.74±0.55 mm vs. 2.71±0.49 mm, p=0.41). In histological studies, the luminal surface of all the segments was covered by mature endothelium providing a smooth surface. Compression of the media was detected at the sites of stent struts. In several sites, the internal elastic membrane was injured and the arterial media was lacerated. In both groups, occasional ridges in the luminal surface consisting of smooth muscle cells and extracellular connective tissue matrix were seen. In sections with heated stents, minimal smooth muscle cell proliferation along with extracellular matrix was observed in the neo-intimal layer. However, at the adjacent proximal and distal nonstented segments, regions with intimal hyperplasia were observed. Morphometric studies showed that the mean luminal area was similar in the two groups 4 weeks after the implantation (heated group: 21.9±4.3 µm² vs. control group: 24.8±5.1 µm², p=0.43). The mean maximal intimal thickness was greater in the control group compared with heated segments (93.3±33.6 µm vs. 183.8±51.3 µm, p=0.04). The mean thickness of the arterial media was less in the heated segments as compared with nonstented segments (65.6±13.1 µm vs. 112±25.7 µm, p=0.02).

This study demonstrated that metallic stents may be successfully heated up to 50 °C in vitro and in vivo. At 25 cm by using magnetic force. Thrombosis of the stented segment was observed at high temperatures. At a temperature of 43 °C, in-stent intimal hyperplasia was reduced compared to nonstented segments. However, an increased hyperplastic response was detected at the edges of the stents.

A reason for concern in this method is the transmission of heat to the arterial wall. Ideally, heat should be homogeneously transmitted from the struts of the stent to the arterial wall. However, it seems that the hyperplastic response is reduced close to the struts of the stent, an increased proliferative response is observed at the edges of the stent. Thus, it seems that close to the metallic struts, heat is distributed with favorable effect. In contrast, in areas in which heat is not distributed homogeneously, a hyperplastic response is detected. The range of heat is limited, and although cells behind the stent struts may be well heated by a single dose, cells proximal and distal to the extremity of the stent, and areas injured by the balloon treatment may not be effectively covered by heat.

This method may be useful in preventing the development of in-stent restenosis. The capability for multiple sessions of hyperthermia by thenoninvasive mode during the first months after stent implantation may eliminate the in-stent intimal hyperplasia. Moreover, the method is relatively simple and clinically applicable at low cost. Studies are ongoing at our center with a new system constituting an RF-generator connected to capacitors by a fiber-optic connector. This system provides accurate tuning range, as well as current and voltage control.

Conclusions

There seems to be fair knowledge of the morphology of the atherosclerotic plaque. The pathophysiological mechanisms leading to the progression of stable to unstable syndromes is still under investigation. The role of inflammation seems to be important in this process. Lately, new imaging techniques have been developed for the early detection of vulnerable plaques. Thrombography provides considerable information about the inflammatory process and thus it can be used in clinical practice to evaluate the vulnerability of atherosclerotic plaques. In addition, the use of heat applied either invasively or noninvasively may contribute to the stabilization of vulnerable atherosclerotic plaques.

References

A 64-year old woman presented with a 3-month history of shortness of breath and mild congestive heart failure. She was known to have brady-tachy syndrome for which she underwent radiofrequency ablation of atrioventricular node and permanent pacemaker implantation 6 years back. Echocardiographic picture initially suggested thrombus in the right atrium. However, on careful evaluation, a cavity in interatrial septum partially filled with thrombus was identified (Fig. 1). Color and pulsed wave Doppler demonstrated flow of blood from aorta into the cavity and then into the right atrium through tiny

**Correspondence:** Dr SS Kothari, Additional Professor of Cardiology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029
openings (Fig. 2). Similar findings were obtained on magnetic resonance imaging (MRI) (Fig. 3). On angiography, a small channel close to the origin of right coronary artery leading to the cavity was identified (Fig. 4). The precise reason for this patho-anatomy remains unclear, however, we believe this represented dissection into the interatrial septum. Dissection of aorta into the interatrial septum is rare but has been reported.1–4

In view of very small size of channel supplying blood to the cavity, the patient was taken up for interventional closure by coil embolization. Right coronary artery (RCA) was hooked with 8 F right Judkin’s percutaneous transluminal coronary angioplasty (PTCA) guiding catheter. The patient was anticoagulated with 7000 units of heparin. A 0.014" PTCA guidewire (Hannibal™, Boston Scientific Inc, USA) was placed in the RCA to ensure good access in case it was injured during the procedure. Another 0.018" wire (V 18™, Boston Scientific Inc, USA) was passed through the guiding catheter into the anomalous channel (Fig. 5). A microcatheter (Tracker 18™, Boston Scientific Inc, USA) was passed over V 18™ wire and positioned in the anomalous channel. The 0.018" wire was then removed and 6 steel microcoils (3–5 mm in diameter and 3–4 cm long) were delivered in the anomalous channel through the microcatheter. Post-procedure angiograms showed complete occlusion of the anomalous channel (Fig. 6). Patient was well on follow-up at 6 months and investigations (echocardiography and MRI) revealed that the cavity was completely thrombosed and reduced in size.

References
Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease (ERACI II)

Alfredo Rodriguez et al.  
*J Am Coll Cardiol* 2001; 37: 51–58

### Summary

This multicenter randomized study compared percutaneous angioplasty (PTCA) with stent implantation to coronary artery bypass surgery (CABG) in selected high-risk patients with multivessel disease. Four hundred and fifty patients (92% with unstable angina) were randomized to PTCA with stent implantation v. CABG (225 patients each). The primary endpoints were major adverse clinical events (MACE) – Death, Q-wave myocardial infarction (Q-MI), and the need for repeat revascularization at 1 month and 1 year. At 1 month, PTCA patients had lower MACE than CABG (Death: 0.9% v. 5.7%, p<0.013; nonfatal Q-MI: 0.9% v. 5.7%, p<0.013; MACE: 3.6% v. 12.3%, p<0.002). At follow-up (mean 18.5±6.4 months) patients undergoing PTCA with stent implantation showed better results than patients who had undergone CABG (survival: 96.9% v. 92.5%, p<0.017; freedom from MI: 97.7% v. 93.4%, p<0.017). However, the requirement for repeat revascularization was higher in PTCA with stent group as compared to CABG (16.8% v. 4.8%, p<0.002). This study showed that in the high-risk group of patients with multivessel disease, PTCA with stent implantation group had better survival and freedom from MI compared to the patients who had undergone conventional surgery.

### Comments

Earlier randomized trials which have compared angioplasty with surgery in multivessel disease (ERACI I, RITA, BARI, EAST, GABI and CABRI) have shown that the mortality rates and important clinical outcomes during the follow-up period ranging from one to five years are not significantly different between the two revascularization techniques. However, in all these studies the need for repeat revascularization and recurrence of angina was lower in the surgical group. The present study (ERACI II) is the first to demonstrate a lower mortality and MACE both at 30 days and one year in patients with multivessel disease undergoing PTCA with stent implantation compared to CABG. This has been due to a higher than expected mortality in the surgically treated patients and lower than expected MACE in the PTCA group. The proponents of this study attribute their excellent results to the use of stents in their patients and expect even better results with the concomitant use of glycoprotein IIb/IIIa inhibitors. However, their opponents are unable to accept such a high surgical mortality. They further argue that the numbers are too small to get a robust statistical analysis. The results of the future trials, i.e. stent v. surgery trial (SOS) will provide additional data to answer this important question.

---

Lack of Neointimal Proliferation After Implantation of Sirolimus-Coated Stents in Human Coronary Arteries

J Eduardo Sousa et al.  
*Circulation* 2000; 102: r54–r57

### Summary

The safety and efficacy of stents coated with sirolimus (Rapamune), a cell cycle inhibitor, was determined in a pilot study of 30 patients treated with 2 different formulations of the drug: slow release formulation (>28-day drug release) and fast release formulation (<15-day drug release). Each stent was coated with 140 µg/cm² of sirolimus. The primary end point at 4 months was angiographic and intravascular ultrasound (IVUS) analysis for intimal hyperplasia and restenosis. The secondary end points were major adverse clinical events (MACE) – death, myocardial infarction and repeat revascularization at 8 months. There was no restenosis at four-month angiographic follow-up, while only 3 patients showed about 15% intimal hyperplasia on IVUS. No major adverse clinical events or stent thrombosis was noted at 8 months. This is the first human experience with the implantation of sirolimus-coated stents and have shown 0% restenosis with minimal or no intimal hyperplasia on follow up.

### Comments

Various pharmacological approaches to prevent restenosis have not been successful, possibly due to insufficient local drug concentration. In order to overcome this problem, polymeric-coated stents have been advocated. In this elegantly performed small study, the authors have shown 0% restenosis in de novo lesions (<18 mm with diameter of 3.0–3.5 mm) by sirolimus-coated stents. The minimal amount of intimal hyperplasia in the present study (10.7%) and almost 0% late loss, seems remarkable compared to previous reports. The intimal hyperplasia in noncoated stents ranges from 19% to 48% and lumen loss is 0.8 to 0.9 mm. Although the radioactive stents have shown an intimal hyperplasia of 7%–17%, they are limited by edge restenosis and late thrombosis. These side-effects were absent in the sirolimus-coated stents. This is a small study and the results need to be validated in larger, prospective randomized trials. Further, 12 month angiographic follow-up is lacking. Other drug coatings; taxol, phosphorylcholine, heparin and paclitaxol are being studied. Further, newer strategies to reduce restenosis include cryotherapy, sonotherapy, photodynamic therapy and the use of coated and biodegradable stents.
Hemodynamic Effects of Sildenafil in Men with Severe Coronary Artery Disease

Summary
The cardiovascular effects of sildenafil (Viagra, Pfizer) are important as patients being treated for erectile dysfunction are usually in the age group of coronary artery disease. In the present study, systemic, pulmonary and coronary hemodynamic effects of oral sildenafil (100 mg) were studied in 14 men (mean age: 61 years) with severe stenosis of at least one coronary artery. Coronary blood flow velocity and flow reserve were determined with a Doppler guidewire and maximal hyperemia was induced with intracoronary administration of adenosine both before and after sildenafil. Oral sildenafil caused a small (<10%) decrease in systemic and pulmonary arterial pressures. It had no effect on the pulmonary capillary wedge pressure, right atrial pressure, heart rate or cardiac output. Double product (heart rate times systolic blood pressure) fell significantly from 9435±1739 mmHg per minute to 8641±1722 mmHg per minute (p=0.02). There were no significant changes in average peak coronary flow velocity, coronary artery diameter, volumetric coronary blood flow or coronary vascular resistance. The coronary flow reserve increased about 13% in stenosed and reference arteries after the administration of sildenafil. In both groups of arteries combined, it increased from 1.70±0.59 to 1.92±0.72 (p=0.003). In this study, no adverse cardiovascular effects of oral sildenafil were observed in men with severe coronary artery disease.

Comments
Men with erectile dysfunction may also have cardiovascular disease, as some of the risk factors are common for both conditions. Further, serious cardiovascular events including myocardial infarction and sudden death have been temporally correlated with sildenafil use in the past. However, this study demonstrates that oral sildenafil has no direct adverse cardiovascular effects in men with severe coronary artery disease and may have a small positive effect on coronary blood flow reserve. This data supports the ACC/AHA consensus view that sildenafil is safe for patients with stable coronary artery disease who are not taking other medications containing nitrates.

Endoluminal Beta-Radiation Therapy for the Prevention of Coronary Restenosis after Balloon Angioplasty

Summary
In this prospective randomized, multicenter, dose-finding study using beta radiation (Yttrium – 90), 181 patients were randomized to receive 9, 12, 15 and 18 Gy at a tissue depth of 1 mm following successful angioplasty of a previously untreated coronary artery. Adjunctive stenting was required in 28% of the patients. The primary end-point was the minimal luminal diameter (MLD) at 6 month follow-up angiography and the secondary end-points were death, myocardial infarction (MI), coronary artery bypass grafting (CABG) and target vessel revascularization (TVR). The results showed that MLD was maximum with a dose of 18 Gy, and there was a dose dependent increase in MLD of at least one coronary artery. Coronary blood flow velocity and flow reserve were determined with a Doppler guidewire and maximal hyperemia was induced with intracoronary administration of adenosine both before and after sildenafil. Oral sildenafil caused a small (<10%) decrease in systemic and pulmonary arterial pressures. It had no effect on the pulmonary capillary wedge pressure, right atrial pressure, heart rate or cardiac output. Double product (heart rate times systolic blood pressure) fell significantly from 9435±1739 mmHg per minute to 8641±1722 mmHg per minute (p=0.02). There were no significant changes in average peak coronary flow velocity, coronary artery diameter, volumetric coronary blood flow or coronary vascular resistance. The coronary flow reserve increased about 13% in stenosed and reference arteries after the administration of sildenafil. In both groups of arteries combined, it increased from 1.70±0.59 to 1.92±0.72 (p=0.003). In this study, no adverse cardiovascular effects of oral sildenafil were observed in men with severe coronary artery disease.

Comments
Men with erectile dysfunction may also have cardiovascular disease, as some of the risk factors are common for both conditions. Further, serious cardiovascular events including myocardial infarction and sudden death have been temporally correlated with sildenafil use in the past. However, this study demonstrates that oral sildenafil has no direct adverse cardiovascular effects in men with severe coronary artery disease and may have a small positive effect on coronary blood flow reserve. This data supports the ACC/AHA consensus view that sildenafil is safe for patients with stable coronary artery disease who are not taking other medications containing nitrates.
### Calendar of Conferences

**May 2–5, 2001, NASPE's 22nd Annual Scientific Sessions, Boston Massachusetts, USA**  
Contact: Mark H Schoenfeld, NASPE, Six Strathmore Road, Natick, MA 01760-2499, USA  
Fax: 508-647-0124, e-mail: info@naspe.org  
Website: www.naspe.org

**May 22–25, 2001, Pediatric Interventional Cardiac Symposium, Metro Convention Center, Toronto, Canada**  
Contact: Course Director: Dr Ziyad M Hijazi  
Website: www.picsymposium.com  
Fax: +1 978 475 1333

**May 27–31, 2001, 3rd World Congress of Pediatric Cardiology and Cardiovascular Surgery, Toronto, Ontario, Canada**  
Contact: Dr Robert M Freedom, Division of Cardiology, Hospital for Sick Children, University of Toronto, Faculty of Medicine, 555 University Ave, Toronto, Ontario M5G 1X8, Canada  
Fax: 1 416 813 7547

**June 24–27, 2001, 4th International Meeting on Interventional Cardiology, Tel Aviv, Israel**  
Contact: The Secretariat, 4th International Meeting on Interventional Cardiology  
P.O. Box 50006, Tel Aviv 61500, Israel  
Fax: 972 3 517 5674, e-mail: intercard4@kenes.com

Contact: The Secretariat, Washington State Convention Center, Seattle, WA, USA  
Website: www.asecho.org

**July 6–11, 2001, XVII World Congress of the International Society for Heart Research, Winnipeg, Manitoba, Canada**  
Contact: Institute of Cardiovascular Sciences, St. Boniface General Hospital Research Centre, University of Manitoba, Faculty of Medicine, 351 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada  
Fax: 1 204 233 6723, e-mail: ishr@cc.umanitoba.ca

**July 29–Aug 10, 2001, 27th 10-Day Seminar on the Epidemiology and Prevention of Cardiovascular Diseases, Granlibakken Conference Centre, Tahoe, CA**  
Contact: David C Goff Jr, Seminar Director, c/o American Heart Association, 7272 Greenville Avenue, Dallas, Texas 75231, USA.  
Fax: 1-214-373-3406

**September 1–5, 2001, XXIII Congress of the European Society of Cardiology, Stockholm, Sweden**  
Contact: European Congress Organization (ECOR), The European Heart House, Stockholm, Sweden,  
Fax: 33 4 9294 7620, e-mail: scientific@escardio.org

**October 3–6, 2001, 13th Asia-Pacific Congress of Cardiology, Manila, Philippines**  
Contact: Dr Noe A Babilonia, Chairman, Organizing Committee, 13th APCC, Suite 1108, 11th Floor, East Tower, PSE Centre, Exchange Road, Ortigas Commercial Complex, Pasig City, Manila 1605, Philippines, Fax: 632 634 7441

**October 13–16, 2001, VII Asian-Pacific Symposium on Cardiac Pacing and Electrophysiology, Beijing, China**  
Contact: Dr Hu Da Yi, Secretary-General, VII APSPE, Beijing Red Cross Chaoyang Hospital  
8 Baijiazhang Road, ChaoYang District, Beijing 100020, People's Republic of China  
Fax: 86 10 6593 7858, e-mail: heart@bme-cspe.org

**November 11–14, 2001, 74th Scientific Session, American Heart Association, Anaheim, California, USA**  
Contact: American Heart Association, 7320, Greenville Avenue, Dallas, Texas 75231, USA  
Fax: 1 214 373 3406

**February 8–10, 2002, VIth World Congress of Echocardiography and Vascular Ultrasound, New Delhi, India**  
Contact: Dr (Col) SK Parashar, Secretary General, C-144, Sarita Vihar, New Delhi - 110044,  
Fax: 6 942222, e-mail: parashar@del6.vsnl.net.in

**March 17–20, 2002, 51st Annual Scientific Sessions, American College of Cardiology, Atlanta, Georgia, USA**  
Contact: American College of Cardiology, 9111 Old Georgetown Road, Bethesda, MD 20814, USA,  
Fax: 1 301 897 9745

**May 5–9, 2002, XIV World Congress of Cardiology, Sydney, Australia**  
Contact: The Congress Secretariat, QVB Post Office Locked Bag Q4002, Sydney, NSW 1230, Australia,  
Fax: 61 2 9290 2400, e-mail: wcc@icms.com.au