Computer assisted management and nomenclatures in congenital heart disease

A clinical and research approach

Freek van den Heuvel

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Computer assisted management and nomenclatures in congenital heart disease. A clinical and research approach

Computer ondersteunde ontwikkeling van behandelingsstrategieën en nomenclaturen op het gebied van aangeboren hartafwijkingen. Een klinische en onderzoeksgerichte benadering

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Voor Mieke
Voor mijn ouders en broer

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Introduction 1

1.1 Clinical management models

Over the last decades major improvements in the diagnosis and management of patients with congenital heart disease have been achieved [1-5]. These improvements have been the result of both evolved insights in the aetiology and pathogenesis aspects of congenital heart disease [6-17] and advances in the diagnosis [18-32] and treatment of congenital cardiac abnormalities [33-71]. As a result the life expectancy of infants born with congenital cardiac defects has increased dramatically [72-77].

New and improved techniques for diagnosis and treatment are introduced in rapid succession. However, in many cases, mainly due to this rapid introduction, thorough evaluation of new techniques is only scarcely performed and prospective randomized clinical trials are often lacking. This has led to the current absence of uniform standards for the diagnosis and management of congenital heart disease. The results of (long-term) follow-up studies [78-106] and the few studies that do investigate the effects of different diagnostic and treatment modalities on outcome [107-109] clearly illustrate the need for development of management strategies [110-112].

As a result of the rapidity by which new diagnostic and treatment approaches are introduced, the speed by which the necessary evaluation studies can be completed has become critical. This need for expeditious evaluation has necessitated development and application of (computer-based) techniques that support this. There-

fore, standardized and uniform recording of patient data is of prime importance. For this, a nomenclature that enables recording and retrieval of these data, both of individual patients and of study groups, is essential.

1.2 Uniform description of congenital heart disease entities and management

Several aspects are involved when trying to capture the complexity of the congenital heart disease domain in a nomenclature. Coverage of the morphologic spectrum in a nomenclature alone is far from sufficient; comprehensive description of techniques for diagnosis, management, and their outcome are a prerequisite. The relationships between morphologic cardiovascular abnormalities and their pathophysiologic consequences have to be made explicit. To realize this, domain coverage and the physiological consequences of morphological abnormalities have to be situated in the context of these clinical entities.

The broad spectrum of morphologic congenital cardiovascular entities and the variability in physiologic presentation and severity within these entities is characteristic of the congenital heart disease domain. This complexity and large inter-individual variability seriously limits the potential for identification of homogeneous study populations.

Several different coding schemes have been developed in order to capture the congenital heart disease domain in coded form. However, these schemes only partially meet the requirements of clinical orientation and domain coverage. Consequently, their value for the support of both uniform, entity-based collection of patient data and subsequent identification of study groups is limited.

1.2.1 Computer based support of clinical management

The complexity and size of the congenital cardiac domain, not only with respect to nomenclature but also with respect to the patient data collections required and the need for rapid solution of research queries made the choice for a computer based approach obvious.

During the last decade, development and application of medical information technology in clinical medicine has become more and more important. Within the field of medical informatics research, currently much effort is put into methodology for capturing medical patient data in its full complexity. From this research the insight has emerged that in addition to capturing the "language" (the nomenclature) that is used in clinical medicine, capturing the clinical context in which nomenclature is used and in which patient data arises is of equally fundamental importance. Controlled entry of patient data is a prerequisite in order to achieve the high quality of data necessary to carry out management studies as intended here. Although progress has been made, in many aspects the developments are still in their earliest stages and standards are generally lacking.

1.3 Aim of the thesis

The aim of this thesis is to investigate the feasibility and the potential value of medical information technology applied to the support of research into evaluation and development of management strategies for patients with congenital heart disease. Evidently such a project requires a close collaboration between clinicians and researchers from this highly specialized medical domain on the one hand and workers in medical informatics on the other hand.

The interaction between these two disciplines is reflected in the sections of which this thesis is composed. Firstly, a terminology based on domain nomenclature and knowledge to organize nomenclature and support both collection and subsequent analysis of patient data was developed. Emphasis was put on structuring nomenclature according to congenital heart disease entities as encountered in clinical practice, and recent developments in congenital cardiology were included. Secondly, we investigated how this terminology and formalized medical knowledge could be incorporated into a computerized system which enables both controlled entry of patient data and retrieval of data of individual patients and study groups. Finally, our first experiences with the terminology system for support of research and development of clinical management models for patients suffering from congenital heart disease are presented, with three studies on congenital heart disease entities as examples.

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Part 1
Methodology

Classification and coding of congenital heart disease

2

2.1 Introduction

There is an increasing need for standardized and accurate storage of patient data as coded information in computer processable form [1-8]. To a substantial extent this increasing need has developed from a change in purpose from use of coded data for administrative, statistical, and epidemiological purposes towards use of these data for both fundamental and clinical research and, more recently, the development and evaluation of management strategies (care guidelines, clinical pathways) [9-12]. These changes have increased the requirements for coding schemes capable of abstraction of patient data into a manageable format with the required completeness and level of detail [13]. Research in medical informatics has shown that more advanced terminology systems than the coding schemes that have traditionally been used are needed to realize adequate support of both the data collection process and its subsequent retrieval and manipulation [5, 13-15].

Over the last decades our knowledge on the understanding and diagnosis of congenital heart disease has expanded substantially. Both fundamental research, that advanced our understanding of the etiology and pathogenesis of congenital cardiac abnormalities, as well as introduction of new or improved diagnostic techniques such as cross-sectional and Doppler echocardiography and MRI have contributed to this. One consequence of this is that the need for detailed, clinically oriented descriptional methods has increased considerably. In order to realize such a clini-

cally oriented description, these clinical aspects have to be made explicit. Placement of morphologic abnormalities in their clinical context and relation of clinical, pathophysiological aspects of congenital heart disease to structural cardiac abnormalities are essential in this and constitute two important difficulties to be solved.

In pediatric cardiology there is a strong need for a system that is capable of both storage and retrieval of the many aspects related to the study and management of patients with congenital cardiac malformations [16, 17]. This need is not confined to pediatric cardiology, but also significant to adult cardiology. As a result of the substantial improvements in the management of patients with congenital cardiac abnormalities over the last decades, a growing group of patients, traditionally managed within the domain of pediatric cardiology, are being referred to adult cardiology for further management. As a result this care is becoming an increasingly important area of adult cardiology. Many of the long-term consequences of managed congenital cardiac abnormalities are still unknown, which emphasizes the need for research in this domain.

The need for accurate and uniform registration of congenital heart abnormalities is not only felt within the domain, but also by those working in other areas of medical research [18]. Research into molecular biologic aspects of congenital (cardiac) abnormalities is but one example where close co-operation between other medical disciplines and congenital cardiology is required.

We have developed a new terminology system for the support of clinical research in this domain [19, 20]. Central to this system is a comprehensive terminology of congenital heart disease nomenclature. An important part of this nomenclature deals with the morphologic description of congenital cardiac malformations. It is based on one of the two generally accepted approaches to morphologic description which are currently used. In this paper we will review the historical developments that have led to the current insights and approaches to the description of congenital cardiac abnormalities. In addition it is described how these developments have found there way into several coding schemes and which major problems and limitations are involved in the use of these schemes.

2.2 Morphologic classification of congenital heart disease

In this section an overview is given of the two main methodologies that are developed for morphologic description of congenital heart disease. After that an inventory is made of the problems, from a medical terminological point of view, that still obstruct unambiguous description of congenital cardiovascular abnormalities. This section focuses on methodology. How these approaches have found their way in coding schemes and the problems that are involved in computer-based collection and manipulation of these data is the subject of the following section.

2.2.1 Evolution of the morphologic approach

The principles of our current insight in the diagnosis and description of morphologic abnormalities are almost entirely based on the concepts of the segmental analysis that originated in the work of Van Praagh et al. [21-24]. Over time several major revisions were introduced and as a result of a fundamental difference in opinion between two groups of morphologists a separation occurred that has resulted into two major approaches.

2.2.1.1 The segmental approach, the "American school"

The original concept of the segmental approach to the diagnosis of congenital heart abnormalities was based on the position and orientation, also designated as the situs, of the main cardiac segments that make up the heart [21-23, 25-27]. In this approach these segments consisting of the atria, ventricles, and great arteries are viewed as the elements of a set. Within such a set a single character abbreviation was used to represent the situs of the corresponding set element. These abbreviations, ordered to reflect a logical veno-arterial organization were enclosed by a pair of brackets: {atrial situs, ventricular, great-arterial situs}. During the first decade after introduction of this concept, emphasis was mainly put on the spatial relationships of these main cardiac segments. The connections between these cardiac segments were deduced from these spatial relationships by means of the "loop-rule".

During its evolution two connecting segments were added to the main cardiac segments [28, 29]. The first connecting segment, the atrioventricular canal or atrioventricular junction, connects the atria with the ventricles. The second, the infundibulum or conus, forming the connection between the ventricles and the great arteries.

Descriptions of morphologic abnormalities based on the original situs description set were hence extended with descriptions of these two connecting segments. This introduction of connecting segments constitutes the most important and major change in the original segmental approach. It was introduced because in some cases the internal organization of the ventricles were found to be predicted erroneously when the type of atrioventricular connection was deduced from the situs descriptions alone [30, 31]. Also a distinction was made between the alignment and connection aspects of the connecting segments. This distinction was found to be essential for anatomic accuracy, but others have argued that this distinction is unclear and artificial [32]. Introduction of the concept co-occurred with publications on cardiac segmental connections by others [33, 34].

Over time many other changes were introduced both in emphasis and substance [24] often in response to criticism by others. A change was made in the original definition of the D-loop and L-loop [35], which was necessary for the description of unusual ventricular relationships [36, 37]. Other perceived deficiencies were based on descriptions of hearts with a double outlet left atrium [38, 39] whereas the Van Praagh methodology only described double outlet right atrium. Also no distinction could be made between atresia of the atrioventricular valves as a result from total absence of the atrioventricular connection or atresia resulting from an imperforate valve.

2.2.1.2 The connexion approach, the "European school"

Over time, commentary and criticism on the segmental approach resulted in an alternative morphology based nomenclature [33, 34, 37, 40-46]. Fundamental to the approach of the so called "European school" was the emphasis on connections rather than on segments. Although the main cardiac segments are recognized, identification of the type of interconnection between the cardiac segments is central in the "connexion" approach. Descriptions of spatial relationships are documented, but they are an addition to the description of atrioventricular and ventriculo-arterial connection.

This morphologic method too has evolved and several major and minor evolutionary changes were made. The most important change that was made in the method as it was introduced, constituted revision of the principle of the single ventricle.

This principle was based on the assumption that in some cardiac anomalies it was correct to describe the combination of a dominant and rudimentary ventricle as a single ventricle system [21, 41, 47-49]. It was met with criticism [28, 50, 51]. This fundamental idea of the univentricular heart was replaced by the concept of ventricles and non-ventricles. However, this modification still proved to be problematic in describing some congenital abnormalities such as hearts with overriding atrioventricular valves. In these cases the amount of overriding of the atrioventricular valve orifice was used in the "50 percent rule" to determine which of the two ventricles was to be considered a non-ventricle rather than a ventricle [47], although they might be nearly identical.

This methodological problem was solved by introduction of the univentricular or absent atrioventricular connection instead of assuming the ventricular complex to be univentricular [52, 53]. In this view all chambers of the ventricular mass were now recognized and described as ventricles, irrespective of their size, topology, or position. However, situations remained where this principle could not be used unambiguously [54, 55]. They were related to cases of a double outlet atrium [56-58] that cannot be described with the univentricular atrioventricular connection concept, because although the atrial side of the connection is of univentricular character, the ventricular side of the connection is biventricular. Or related to cases of absent right atrioventricular connections in which in contradiction to classical cases of absent right atrioventricular connection, it was not the continuity between the morphologically right atrium and right ventricule that was missing, "tricuspid atresia", but the absent connection appeared to involve the right atrium and a morphologically left ventricle and the lesion could be regarded as "mitral atresia". The presence of such cases was debated [59], but shown to exist and the addition of a description of the concordant or discordant nature of the absent connexion proposed as a solution to further clarify the absent atrioventricular connexion concept [54].

2.2.2 Issues in the description of cardiac morphology

Problems that still prevent unambiguous description of (complex) heart abnormalities are not only related to the use of the different approaches to the sequential morphologic description of hearts, but also to the use of nomenclature and concepts that have become obsolete. Another order of problems is related to the different interpretation of a single concept by the different disciplines involved. Fi-

nally, there are obstacles from a linguistic view point which may result in confusion and incorrect interpretation, such as persistent use of proper names, obsolete or unclear names and synonyms.

The primary purpose of this section is to illustrate the difficulties encountered in the "translation" between clinically encountered congenital heart disease entities and strictly morphological principles. Such difficulties result from the fact that for some abnormalities, which are regarded as completely different when seen from a strictly morphological viewpoint, this distinction is of limited value from a clinical, pathophysiological point of view. In order to achieve suitability of a coding system based on morphological principles for use in the clinical setting, such differences have to be solved.

2.2.2.1 Application of different approaches to the sequential analysis

Despite their separation, both schools of approach to the sequential morphologic analysis have continued to evolve and have benefited from each other. Both approaches are used in the medical literature. The result of this is that although both systems are comparable with respect to major aspects, differences in the interpretation and description of minor aspects of complex congenital abnormalities persist. Added to the differences in linguistic aspects of the nomenclature used by both approaches, this has led to the unfortunate situation that understanding and correct interpretation of studies still require substantial knowledge of both approaches. Things become more problematic when insights that have been recognized as obsolete are still being used by others.

2.2.2.2 Other problems in description of cardiac morphology

A different area of problems in the description of congenital heart lesions, is the use of terminology that is based on "classical" concepts of embryological development of the heart that have been shown erroneous over time, such as the single ventricle concept [60-62]. Another example is the group of lesions commonly described as the endocardial cushion defects. In these descriptions the defects in both formation of the tricuspid and mitral valve as well as components of the interatrial and interventricular septum were thought to result from failure of fusion of presumed common developmental components. Later, these assumptions were shown

to be incorrect [63] and it was suggested to describe these lesions as atrioventricular septal defects instead [64-66].

Other potential sources of confusion are related to differences in understanding that result from different viewpoints. An example of this is tricuspid atresia. Classical tricuspid atresia has been assumed to result from an imperforate, atretic tricuspid valve [67]. Others however, have argued that this abnormality is the result of complete absence of the right atrioventricular connection. Although several studies have supported this absence of the atrioventricular connection in favor of valve atresia [68-71], the term tricuspid atresia remains in use [72, 73]. From a clinical point of view, the difference between an atretic valve or genuine absence of the atrioventricular connection may be completely irrelevant because both situations produce the same hemodynamic effects.

2.3 Coding of congenital heart disease

The aim of the coding process is to obtain an abstraction of all relevant aspects of patient data from its original source, the paper medical record. Which data and by what means these data are abstracted, are to a large extend determined by the purpose for which these (coded) data are collected.

2.3.1 Schemes for coding of congenital cardiac abnormalities

In parallel with development of the morphologic approaches to the description of congenital cardiac malformations several coding schemes were developed. These domain specific coding schemes have remained paper-based, with the exception of the Moulaert coding system [74]. Also several coding systems developed for use in general medicine exist that incorporate aspects of congenital cardiology.

2.3.1.1 Coding schemes for congenital cardiology

Based on the Systematized Nomenclature of Pathology (SNOP) [75] an extension of specific parts of the SNOP, relevant to congenital cardiology, was developed [76]. The structure of the extension was similar to that of SNOP and allowed abstraction of patient data using enumerated terms organized into "axes" on topology (anatomy), morphology (lesions), etiology, procedures and function. Because of its

origin the general characteristics, and associated disadvantages of the extension were identical to those of SNOP. The extension permitted coding of morphologic abnormalities to a high level of detail. For those situations where a required term was not available, the scheme permitted combination of "atomic" elements into the required term by means of a process known as combinatorial extension. Although this property allows highly detailed and accurate descriptions of congenital cardiac aspects to be made almost at a linguistic level, this also constitutes a major disadvantage. Description of a single aspect can usually be done in many different ways which results in redundancy. Redundancy, having more than one term available for the description of the same medical concept, is generally recognized as a major limitation of codings schemes that use a similar method of description. An example of which is SNOMED international [77], a currently standard nomenclature that covers all of medicine and has its ancestry in the SNOP.

The Van Mierop coding scheme, published in 1984 was based on the Van Praagh segmental approach and accomplished through a consensus process extended over several centers [17]. To overcome problems of redundancy a systematic approach was applied. Although the scheme was based on the segmental approach of Van Praagh it did not strictly follow the organization determined by this approach. Terms for intrasegmental descriptions were mixed with aspects of cardiac segments and intersegmental alignment. In several areas the detail provided was not sufficient and terms for description of surgical procedures and complications were generally lacking. In the scheme several ambiguities were present where single terms could be used for the description of various different abnormalities. By means of appending additional terms, the meaning of these ambiguous terms could be modified or extended. However, information on clinical context that was necessary for correct interpretation of these combinations of codes was lacking.

The Brompton Hospital diagnostic coding scheme was published in 1985 [78]. The organization of this scheme is comparable to the Van Mierop scheme, but was based on the concepts of the "European" sequential connexion approach. The scheme's intentions were only to provide for codes relevant to the sequential morphologic description. Therefore terms on all other aspects of congenital cardiac abnormalities were not included.

The scheme developed by Weinberg [16] was based on the segmental approach of the Van Praagh school. It was the first scheme to accommodate the notion that description of congenital cardiac abnormalities should be based on clinical "entities" rather than on "nomenclature". This was based on the assumption that variation in entities for the description of cardiac deformities was far less than the variation in nomenclature. Several additions and changes to the original descriptions of Van Praagh were introduced. Where mutually exclusive diagnostic concepts existed, correct coding was promoted by means of cross tables that contained only valid combinations of concepts depicted as schematic drawings. Also terms were present for the description of treatment and postoperative complications. This scheme also introduced "cross referencing" as a solution to difficulty of term placement in cases were a single terms could be placed at more than one location with equal validity. Cross referencing is also known as multiple classification.

Based on the Brompton Hospital scheme, a comprehensive coding system was developed by Moulaert et al. for application in a pediatric cardiology database management system, PCDBMS [74]. This database system was developed specifically for the support of research on patients with congenital heart disease and has been used for several years in most Dutch pediatric cardiology centers, as well as in several centers outside the Netherlands. In addition to morphology and sections on management, complications, and electrophysiology several sections for the description of associated abnormalities, both cardiac and non-cardiac related, that could be found in (pediatric) patients were present. With respect to its contents the coding scheme provided acceptable coverage of both the congenital cardiology domain and, in its most recent release, the cardiothoracic domain. However, several problems mainly related to the structure and implementation of the coding scheme, as well as problems related to the database system itself obstructed successful use of the system for follow-up research. The systematic, but non-clinical organization and highly detailed nature of the 3800 vocabulary terms rendered coding of patient data time-consuming and difficult. Also identification of populations for research based on more generic diagnostic or management criteria from these highly detailed coded data proved virtually impossible.

2.3.1.2 *Coding schemes for larger domains or general medicine.*

Several coding schemes have been developed for use in larger domains of clinical medicine. The most relevant generic coding schemes are the ICD-9-CM [79] and the recent release of ICD-10 [80], SNOMED international [77], the Read Clinical Codes version 3.1 [81] and the Gabrieli Nomenclature [82]. Although some of them are comprehensive for application within the domain they have been developed for, general medicine, their contents are generally too limited for use in congenital cardiology beyond epidemiological purposes. Usually their coverage of the congenital cardiac domain is fragmentary and incomplete. Also, in a number of situations the items in these generic coding schemes are derived from obsolete morphological principles and nomenclature.

2.3.2 Aspects related to the use of coding systems in congenital cardiology

Although the generic medical coding schemes mentioned in the previous section in themselves are not suitable for application in our domain, significant experience with the use of such schemes was gained in both (general) clinical practice and research environments, especially with SNOMED and ICD. These experiences together with research on improvement of both the contents and structure of such systems have substantially extended our knowledge on coding and terminology. This knowledge is equally valuable for the development of a suitable coding system for use in a highly specialized domain of medicine, congenital cardiology, as it is for coding systems on general medicine. Based on this knowledge together with the understanding that collection and retrieval of patient data are inherently different processes, several characteristics are apprehend which determine the suitability of a coding system for abstraction and (subsequent) analysis of coded patient data.

2.3.2.1 *Domain coverage and completeness*

An important requisite for effective use of a coding system in a specific domain, is that it provides good coverage of this domain. Coverage not only relates to the breadth of the domain but also to the level of detail (granularity) it provides. Furthermore, when a coding system is to be used for clinical follow-up research incorporation of terminology on management, complications, and related disease areas becomes essential. Morphology is covered by all congenital cardiology coding schemes, but only the Weinberg scheme and Moulaert system contain addi-

tional terms on procedures, interventions, and complications. Only the Moulaert system does accommodate sufficient coverage and completeness of the domain.

To retain domain coverage and completeness, facilities for maintenance and extension of coding systems are crucial. Not only to incorporate changing and new or improved techniques for diagnosis and management, but also to ascertain correct dealing with aged and obsolete terms. This is essential to prevent loss of information in historic data when nomenclature changes over time.

2.3.2.2 Contents and expressiveness

A second important property of a coding system is that its contents ought to be non-redundant and non-ambiguous [83]. Both redundancy and ambiguity are significant obstacles for unequivocal interpretation of collected codings, in particular when the context in which these data were abstracted is unknown [84, 85].

Important to the domain of congenital heart disease is which of the sequential morphologic nomenclatures was used for construction of the coding system and at what stage of development the chosen approach was at that time. For instance, only the last version of the Moulaert coding system in the PCDBMS fully incorporated the concept of absent atrioventricular connection from the "European" sequential analysis. Up till then the previous versions still accommodated the principle of the univentricular heart.

Expressiveness of a coding system deals with the facilities that are available to achieve correct, precise, and consistent abstractions of patient data with the coding system contents. Many coding systems only provide precomposed terms, each term describing a (unambiguous) medical concept. In such systems data abstraction is accomplished by selection of the most appropriate codes. To meet situations in which more detail is required, some coding systems provide means for extension of expressiveness through the use of "specify" terms that allow extension of their meaning through the addition of textual descriptions. However, such freetext descriptions have seriously adverse effects on the retrievability of information and are therefore undesirable.

A different approach to increasing expressiveness is the use of combinatorial extension. However, without control over the extension process such an approach easily leads to redundancy. The use of modifiers is a retrained variation of improving expressiveness by means of combinatorial extension. In such an approach, modifiers only attenuate the meaning of (precomposed) terms instead of changing it. When applied in the appropriate way, modifiers offer a suitable means of extending expressiveness without introducing redundancy.

2.3.2.3 Structure and organization

The congenital heart disease coding schemes described in the preceding are all made up of term-identifier pairs structured into a hierarchy. In these situations identifiers or "codes" not only serve to impersonate a specific term, they also determine their position in the hierarchy. Such an approach restricts the number of terms that can be placed in a hierarchy branch, because of numerical limitations in the term identifiers, and is therefore undesirable.

When the hierarchical organization is strict; the same term identifier combination cannot be placed at more than one location in the hierarchy. However, in many situation placement is not straightforward and therefore more than one location is appropriate. An example of this is subaortic stenosis. Valid locations for this term are hierarchy branches on aortic valve as well as left ventricular outflow tract morphology. Only the Weinberg scheme does allow such multiple classification of terms.

Usually, these hierarchies are structured according to morphology. Although such an organization is logical and straightforward from a morphologists point of view, such a structure is unfavorable when used for the description of patients with congenital heart defects. For these situations an organization that reflects the clinical patterns or "entities" of congenital heart disease is advantageous. These clinical entities not only mirror aspects of morphology and pathology encountered in this context, but also comprehend available management options, complications and (potentially) related abnormalities. However, when the same coding system is to be used for research purposes a completely different organization of nomenclature might be required.

Research studies, at least the initial stages of studies that deal with patient groups, require retrieval based on more generic concepts than those represented by the terms in a traditional coding scheme that is intended for abstraction of detailed patient data. To realize the flexibility in level of detail or "granularity" that is necessary for support of both collection and retrieval of coded patient by means of a single coding system, the knowledge on how capture these levels of detail has to be present in the coding system itself. To accomplish this the traditional hierarchy is unsuitable [8, 13, 83, 86].

Finally, when a traditional coding system is used for coding of patient data, making complete and non erroneous abstractions of patient data is completely left to the user. This not only requires a thorough knowledge of the medical (specialty) domain itself, but also of the contents of the coding system. This lack of control over how the elements of a coding system are being used is a major source of non-intentional errors in coded patient data.

2.4 Approach to an advanced coding system in congenital cardiology

One of the most essential steps toward the realization of generic medical abstraction systems that are more appropriate for the current demands on the quality and range of uses for (coded) patient data is abandoning the traditional hierarchical coding system structure and several approaches have been advocated and studied [8, 14, 15, 87, 88]. One such approach is the use of semantic networks for representation of medical concepts and knowledge [15, 89]. In such an approach term identifiers are no longer used as locators, but structure is achieved through specification of relations between term pairs. Such relations represent meaningful characteristics of the relationship between term pair members. Semantic networks have been used successfully for large and complex terminologies covering wide areas of medicine [15, 89]. Their principles apply equally to smaller, more detailed domains of medicine such as congenital cardiology [20].

2.4.1 Use of language for the description of coding and terminology systems

When speaking about coding and terminology systems, invariably the problem arises what language to use to designate its components at various abstraction levels. Currently, several efforts are directed towards the development of such a common language [90, 91]. Although in these proposed standards a clear distinction is made between "term" ("designation by a linguistic expression of a general concept in a special language") or "terminological phrase" ("phrase containing at least one term and a number of other lexical items the choice of which being restricted by the term in question") and "concept" ("unit of thought as an abstraction on the basis of properties common to a set of one or more referents") in several studies this distinction is often not clearly made or not used in a consistent manner. In our work we have used a language that in some respects differs from the work of others. An example of this is the word "term" which we have used to denote a individual vocabulary or terminology item where others would have used the word "concept". The generalization of a "term" is then a "concept-type". In much of the current literature one finds "concept" and "semantic-type" instead of our "term" and "concept-type", respectively. Our choice is motivated by the fact that our starting point has been in an existing clinically relevant nomenclature in congenital heart disease. In such a nomenclature, an individual item is denoted by the immediately obvious "term". Usage of the word "concept" in these cases we have found confusing in practice.

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Controlled coding and retrieval in explicit clinical context

Application of a Smart Classification System, SmaCS, in congenital heart disease

3

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3.1 Introduction

Historically, coding of medical (diagnostic) data using straightforward coding schemes has been performed mainly for administrative (billing of tests, procedures, and interventions), statistical and epidemiological purposes. A gradual change in purpose can be observed from the use of coded data for administrative purposes only toward their use for cost analysis, quality assessment, and medical research. In research the use of available patient data for the evaluation of management strategies or care guidelines [1-4] and clinical pathways [5] is becoming increasingly important. Coded medical data is increasingly collected more routinely and systematically and the need for standards to code this medical data in a uniform and comprehensive way is increasing [6-15]. Current research is aimed at the development of such standards for representation of clinical information, because they do not readily exist [14, 16-20].

Meanwhile, the current "traditional" coding schemes are used in situations that strain these schemes beyond their capabilities [17, 19, 21]. Only when coding schemes are small and straightforward they usually work well; when larger medical domains need to be covered or highly detailed and complex interrelated descriptions

have to be made, problems arise. These problems are the result of both the coding scheme itself, the data that is being collected with it, and the resulting abstractions of this data; data that is limited in detail or accuracy and that is incomplete, ambiguous, or even erroneous severely limits is value [16, 22-27].

Many aspects of medical domain knowledge are implicitly apparent to health care workers and domain experts, but not to computer based systems that have to manipulate this complex information in a meaningful way. Because the traditional coding schemes lack this information inclusion of this knowledge into coding schemes, transforming these into more formally modeled terminology systems, is a prerequisite [13, 14, 18, 20, 28, 29]. In search for more suitable alternatives, semantic networks, conceptual graphs, and approaches based on frames are studied [10, 13, 14, 18, 30-33], sometimes in multi-institutional collaborative projects [18, 20, 31, 32].

In this paper we explore the feasibility of transforming an existing traditional coding scheme on congenital cardiac disease into a flexible terminology system that is based on explicit medical knowledge. The development of a new terminology system described in this paper was initiated in response to limitations perceived in a dedicated PC based database management system [34].

Central was the need for a terminology system capable of supporting both data collection and data retrieval in the domain of congenital cardiovascular disease. This required an approach in which the terminology system contents could be represented in accordance with the clinical context in which it was used. In addition to such flexible nomenclature representation other context specific facilities were introduced to realize optimal support of the inherently different processes of data collection and retrieval. Firstly, a view mechanism to provide a means for restricting representation of terminology to only those aspects relevant in specific clinical situations. Secondly, integrity rules that describe combinatorial aspects among terminology parts to guard completeness and correctness during the patient data abstraction process. Thirdly, facilities to gather detailed terms into the broader concepts needed for retrieval of patients based on generic diagnostic, management, and follow-up criteria. In all this, maintaining backward compatibility with existing coded data was essential.

3.2 Methods

3.2.1 Background

In the domain of congenital cardiology efforts to achieve accurate morphologic description of the complex abnormalities found in children with congenital heart disease have resulted in two generally accepted description methods [35, 36]. To date, morphology and embryology of congenital cardiac abnormalities still are an active field of research, but the principles underlying these methods remain unchallenged.

In the past, several enumerated coding schemes have been developed to facilitate description and identification of cases [37-40]. Almost all of these vocabularies were based exclusively on anatomic and developmental aspects of congenital cardiac abnormalities. None of these coding systems provided complete domain coverage and all had important limitations with respect to structure and organization of the vocabulary items. Furthermore, to our knowledge, these coding systems remained paper-based and thus no experience with computerized data collection and analysis with these coding systems was gained. Weinberg introduced a new coding scheme to meet a number of limitations in the structure and use of existing coding schemes in congenital cardiology [40]. The ideas of a more clinical, disease entity based approach and logical tables to prevent selection of mutually exclusive items were new. However, the proposed scheme itself remained paper-based and met with little follow-up in the literature.

A more or less generally accepted vocabulary, based on one of the two morphologic description methods, is being applied in a PC based database management system for the collection of patient data in Dutch centers for pediatric cardiology and pediatric cardiac surgery since 1989 [34]. The coding scheme contained over 1700 detailed terms for description of morphological abnormalities, management, complications, and a wide range of associated abnormalities in patients with congenital cardiac abnormalities. This database system has been used to maintain a patient oriented registry of highly detailed time-stamped abstractions of diagnostic data and a broad range of encounter and management events on a routine basis. Over a period of 6 years a consecutive series of more than 10.000 patients who presented at the department of pediatric cardiology have been registered in the system and their medical data were coded by a single medically trained person.

Although both the coding scheme and the database system were developed specifically for the support of follow-up research in congenital cardiology, they failed to meet their role in the support of research on this valuable resource. Accurate collection and successive analysis of data for purposes ranging from simple inventories to studies for the identification of optimal treatment strategies for the management of specific groups of patients proved tedious. The strictly hierarchical organization of the coding scheme exclusively based on anatomic principles rather than clinical concepts and a general lack of facilities to support its use and maintenance were identified as the main source of the problems [41].

3.2.2 Aims and considerations

Aims for a new approach were defined based on our experiences with both the original coding scheme and the first experiences with analysis of data that had been collected with it. Central was the need for a single coding scheme to support both controlled collection and subsequent retrieval of collected coded data. To support both processes a coding scheme has to incorporate the required different levels of granularity and provide mechanisms to adapt its organization to the different perspectives on patient data that are required by these processes. Because of the large amount of data that had been collected so far, the contents of such a terminology should be backwards compatible with this data as much as possible to avoid extensive re-coding or loss of data. The system itself should be a "system", not only an environment for the creation and maintenance of terminologies, but also an environment that provides the facilities to support both the collection and successive analysis process. The system was to be generic, providing a terminology environment not only for use in congenital cardiology but also for other similarly detailed and specialized (medical) terminologies. These aspects will be discussed in more detail in the following sections.

3.2.2.1 Controlled data abstraction based on clinical entities

Disease entity descriptions on individual patients require a high level of detail and an organization of the coding scheme contents that reflects the disease entity to be described. In pediatric cardiology, the majority of all congenital heart abnormalities present as more or less circumscribed entities or clinical syndromes. Such an entity can be used as a basis to group only those nomenclature parts that are relevant in the context of this entity into a single representation, reducing the possibil-

ity of making errors. Description of individual patient data should not only be performed in the clinical context of the entity, but the abstraction into coded form should also be controlled, in an effort to further minimize incomplete or erroneous data.

This control is to a large extent determined by the context in which abstraction of patient data takes place. For example, tetralogy of Fallot and coarctation of the aorta are both common congenital cardiovascular disease entities. In both entities a similar group of terms is present that are used for the description of ventricular septal defects (VSDs). They are included in these entities to encompass the variation in cardiac abnormalities that is found within these entities. However, their importance in both contexts is completely different; in tetralogy of Fallot the description of a VSD is obligatory for complete patient description because it is an essential part of the Fallot syndrome. In coarctation of the aorta on the other hand, a VSD can be present as a co-occurring but non-essential, cardiac abnormality.

The coding system uses this context information, represented by the entity, to evaluate completeness and correctness of the coded patient data when terms are selected or existing data are supplemented. Therefore, coded data gathered for a specific patient should always be stored in relation to the context in which they were collected to ensure correct interpretation [42, 43].

3.2.2.2 Data retrieval based on generalizations

Research, at least in its initial stages, usually involves retrieval of data based on more generic criteria. For a coding system with highly detailed terms to be equally suitable for abstraction of patient data as well as for data retrieval it has to incorporate the capability of providing terms on less detailed levels. Such terms are only useful when they are the representatives of broader categories through which detailed terms can be gathered. Again, which terms are represented by such a broad term may depend on the context in which retrieval takes place. Often the context of a research question differs substantially from that used for data abstraction; for example evaluation of a specific management technique that overlaps several disease entities.

3.2.3 Representation of medical knowledge and nomenclature in a semantic network

To realize such a flexible and adaptive coding system a semantic network approach was chosen. In such an approach the various elements of a nomenclature are stored together with various aspects of domain knowledge on this nomenclature. Together they form a terminology; a hybrid of nomenclature and domain knowledge. A semantic network is formed by terms, the individual elements of a nomenclature, interconnected by means of relationships. Medical knowledge is captured by the relations between terms and by the properties, or "attributes" of terms and relations. The structure of such a network is strictly determined by a formal model, also referred to as an ontology [44], of the domain nomenclature. Such an ontology is specified in a concept schema consisting of concept-types and relation-types which are abstractions of the terms and inter-term relations in the anticipated terminology. The attributes of concept-types and relation-types determine the attributes of the terms and inter-term relations they represent.

In our approach both factual and procedural medical domain knowledge are formalized. Factual knowledge is represented by the attribute values of individual terms describing the characteristics of the terms themselves and by their (multiple) relationships with other terms. Especially these (different types of) inter-term relations permit formalization of a wide range of medical aspects; from basic, systematic ones, such as anatomical relationships, to more complex aspects such as those related to the composition of clinical disease entities. Procedural knowledge is represented by what we call "integrity rules". These rules are associated with individual terms and specify their combinatorial aspects.

Relations are directed: relation-type definitions determine their starting (parent) and ending (child) concept-types. A single term may participate in several relations. Members of a term-pair connected by a relation can be instances of different concept-types as well as instances of the same concept-type. These usually indicate broader-narrower relationships. In contrast to relation-types their instances, relations, are acyclic; relations cannot have their starting and ending point in a single term and a term can neither be a parent nor a child of its own. As a consequence a semantic network can incorporate several hierarchies. Individual hierarchies are

accessed by choosing different terms as entry points and following the (directed) relations that are specified. In our approach these multiple hierarchies represent the different contexts.

3.2.4 Other approaches to medical knowledge representation

As mentioned in the introduction, various approaches to the representation of (medical) domain knowledge are currently being studied. These projects differ from each other with respect to the techniques used, their application domain, coverage of the medical domain, and stage of development towards practical application.

Two projects deserve special mention because of their similarity in approach with ours. Both the Unified Medical Language (UMLS) Project [31] and the work on the Medical Entities Dictionary [13] involve terminology systems that make extensive use of semantic networks for the formalization of medical knowledge. However several differences with our approach exist. These differences are not only related to their different interpretation and hence implementation of the semantic network principles, but also to their much broader coverage of the medical domain. They also have different aims. A detailed comparison between our work and these projects will be made in the discussion.

3.3 Implementation of the Smart Classification System

A prototype Smart Classification System, SmaCS, is designed to meet the described requirements. The system consists of two major parts that are represented in figure 3.1; the SmaCS Maintenance System and the SmaCS knowledge base. The prototype SmaCS has been implemented on a HP 9000 series UNIX workstation in C, using embedded SQL for communication with the knowledge base. The knowledge base has been implemented in the Ingres relational database management system and the graphical user-interface has been written in C using the OSF/Motif tool kit.

3.3.1 The SmaCS knowledge base (figure 3.1)

In the knowledge base both the ontologies that define the structure of a terminology as well as the terminology contents are stored. The knowledge base has a 3 layered structure and is implemented as a collection of interrelated database tables. The three layers that make up the knowledge base are the Semantic Concept Schema Layer (SCS Layer), the Terminology Layer, and the Views Layer.

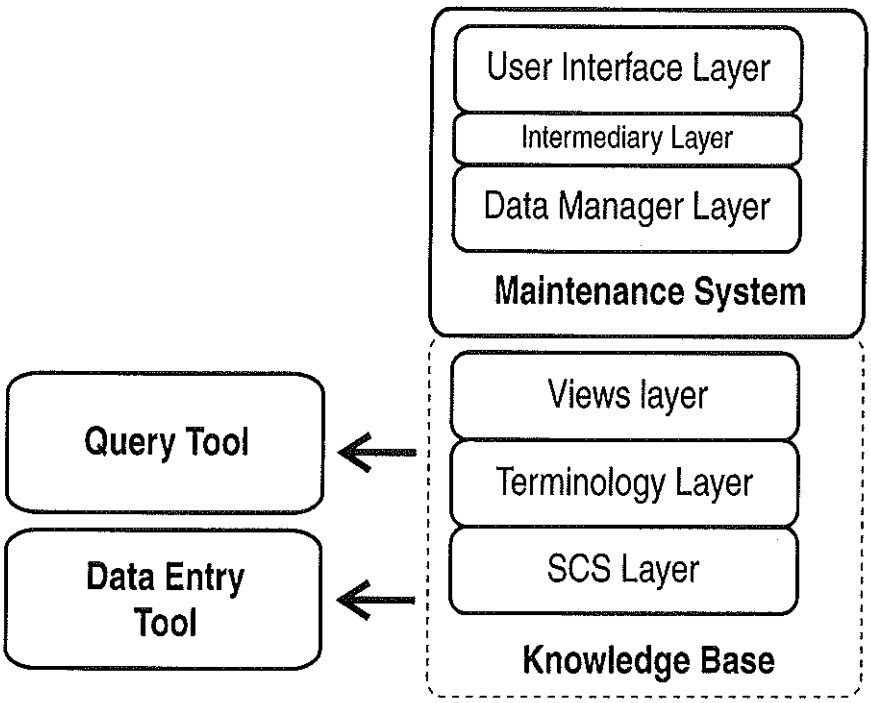

Figure 3.1 : A schematic overview of the Smart Classification System. In the right section of the figure the two main parts of the terminology system are presented: the maintenance system and knowledge base. The left section shows two additional modules: the Query and Data Entry modules. These modules are implemented as separate applications that use the SmaCS system as a "terminology server".

The Maintenance System is implemented as a 3-layered structure: the Datamanager, Intermediary, and User Interface Layer. This construction allows separate re-implementation of individual components. The data manager layer controls interaction with the database management system in which the knowledge base is realized. The intermediary layer controls communication and error-handling between the user-interface layer and the data manager layer and contains the integrity rule parser. On top a graphical user interface has been implemented.

The knowledge base has been realized in the relational database management system, Ingres. Both the tables, the relations specified among them, and the constraints and rules that are necessary for maintaining integrity are stored in the database. These rules are triggered whenever the database is modified, thus insuring the integrity of the knowledge base. This facilitates use of the knowledge base separate from the other SmaCS system components by for example a coding and data analysis module in a dedicated patient database management system. Functionally, the database tables together form a 3 layered structure consisting of the Semantic Concept Schema (SCS), Terminology, and Views layers. These layers are discussed in section 3.3.1.

3.3.1.1 Semantic concept schema (SCS) layer

The bottom layer of the knowledge base is the semantic concept schema (SCS) layer. In this layer, the ontology underlying the terminology is specified as a concept schema consisting of concept-types, representing classes of terms, and relation-types, representing classes of typed and directed relationships between classes of terms. In addition to the attributes that have been predefined by implementation, one or more user-defined attributes may be specified for each concept-type. Each relation-type specifies a directed relation between two concept-types. Cyclic relation-types, relation-types where the starting and ending point are in the same concept-types, are allowed and used for the representation of broader-narrower relationships within the class of terms represented by the concept-type. The resulting concept schema has the structure of a directed graph. In figure 3.2 the definitions are shown of an elementary SCS, used for the prototype congenital heart disease terminology. This prototype new terminology was based on an existing congenital heart disease vocabulary. Therefore the ontology that was conceptualized for the new terminology resulted from a process that made explicit the medical knowledge which was already (implicitly) present in the existing vocabulary; a large part of the "knowledge acquisition" already having been performed by its original creators. The resulting concept schema was extended with the "Clinical Entity" concept-type and three associated relation-types for the specification of medical knowledge aspects related to the representation of clinical disease entities, namely "InvolvesComponent", "InvolvesAbnormality", and "InvolvesManagement" .

3.3.1.2 Terminology layer

On top of the SCS layer is the Terminology layer. In this layer the terms that make up a terminology are stored. A single SCS can be used for several different terminologies. Each term and relation in the terminology layer is related to a concept-

type and relation-type specified in the terminology's SCS. For each term attribute values are instantiated from the corresponding concept-type attributes.

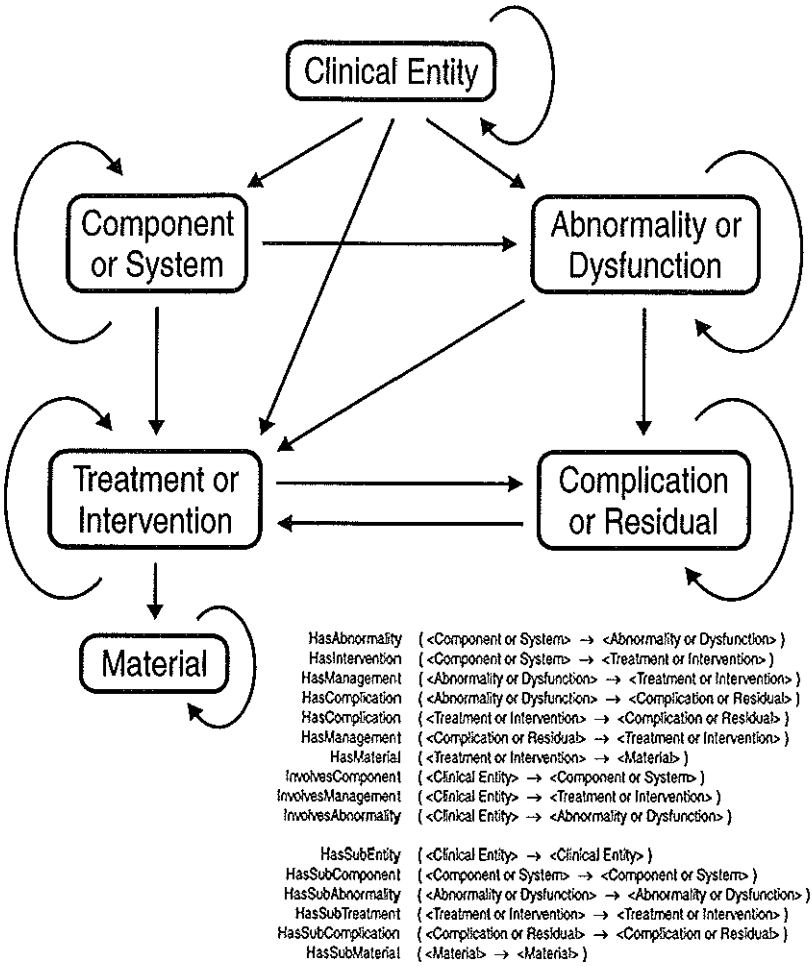

Figure 3.2 : The Semantic Concept Schema consisting of 6 concept-types and 16 relation-types used for the creation of the congenital heart disease terminology. Concept-types are represented by boxes and relation-types by means of straight and curved arrows. The straight arrows represent relation-types between different concepts and are listed in the lower part of the figure. For example, between the concept-types "Treatment or Intervention" and "Material" a "HasMaterial" relation-type has been defined. Curved arrows are relation-types which have both their starting and ending point in the same concept-type, for example the "HasSubTreatment" relation-type present at the concept-type "Treatment or Intervention".

Within a single terminology, terms have unique identifiers. Other attribute values are the term's preferred name and selectable attribute (both obligatory), synonyms, description, modifiers and an integrity rule with accompanying message text (all optional). Integrity rules are described in a subsequent section. The selectable attribute is used to specify whether a term is available for coding during data abstraction. An important application of this attribute is identification of obsolete terms or terms that are introduced in a terminology for grouping purposes only. Rendering obsolete terms non-selectable serves to disable them for data abstraction while maintaining integrity of historic data for data retrieval.

Relations between terms are limited to those relation-types that have been defined in the SCS. Individual terms may be related as a descendent to more than one parent term; this is known as multiple classification. However, specification of relations that result in a cycle are not allowed. As a result the structure of a terminology and its views is that of an acyclic directed graph. In figure 3.3 part of the prototype congenital heart disease terminology is shown in the terminology system maintenance mode.

3.3.1.3 Views layer

Based on the contents of a terminology several views can be defined. There are important differences between a view and the terminology on which its contents are based. The terms within a view are always a subset of the terms in the underlying terminology. Although each member of the view term-subset inherits its attributes and attribute values from the terminology, within a view an alternative name, integrity rule, and selectable attribute can be specified. These alternative attribute values are stored as extensions to the term's terminology attributes and are view specific.

The subset aspect does not apply to view relationships; inter-term relations that differ from those specified between terms in the underlying terminology may be defined, as long as the relation-type they are instantiated from is defined in the SCS.

3.3.1.4 *Rule mechanism*

Integrity rules are logical expressions consisting of term-identifiers and operators used to validate and control data abstraction. In addition to the basic AND, OR, XOR and NOT operators additional functions have been developed to reduce the length and complexity of integrity rules. In figure 3.3, a number of such rules, marked by a "#" symbol in front of term names, are present. One of them is explained in the figure caption.

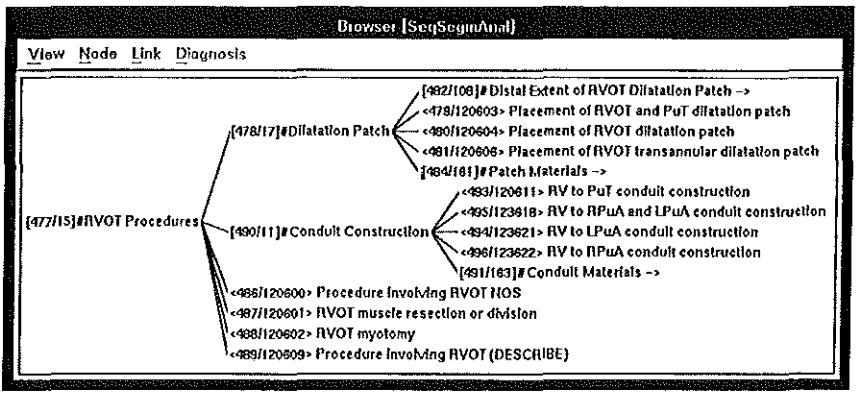

Figure 3.3 : A part of the congenital heart disease terminology shown in the maintenance mode. The terms shown in this branch represent surgical procedures related to the right ventricular outflow tract. In this example the relations between terms are instantiated from two different relation-types, "HasSubTreatment" and "HasMaterial", represented by colored lines (not visible in this figure). Almost all relations are derived from the "HasSubTreatment" relation-type and indicate broader-narrower relations between terms instantiated from the "Treatment" concept-type. Only the terms "Patch Materials" and "Conduit materials", both instances of the concept-type "Material", are linked to their parent terms by means of a "HasMaterial" relation. Three hierarchy levels are shown in this figure. When more detailed terms are available this is indicated by a right arrow at the end of the term name.

In front of each term an internal reference number (first number) and term identifier are shown between either square brackets or a "<>" symbol pair. The latter indicates that the selectable attribute for this term has been set. In our congenital heart disease terminology branch terms (terms which have children) are always non-selectable; leaf terms can be tagged both selectable and non-selectable. After the internal reference / term identifier combination at a number of terms "#" symbols are shown, indicating the presence of integrity rules. An example of such an integrity rule is:

```
Rule at term [490/11]#Conduit Construction
        EXACT( 1, 120611, 123618, 123621, 123622 ) AND 163
```

This rule enforces that when selections are made in this branch a description of a "RVOT conduit construction" surgical procedure is valid only if both the procedure itself (coded as exactly one of the available options) and the conduit material used in this procedure have been specified.

3.4 The prototype congenital heart disease terminology

Based on the semantic concept schema in figure 3.2 a new congenital heart disease terminology has been built. In a single terminology based on this schema all terms from the existing coding scheme were incorporated as instances of the appropriate concept-types. The terminology contents were modified and extended to compensate for erroneous and missing nomenclature areas or to incorporate changed and new insights. Also a substantial number of terms representing more generic medical concepts (of coarser granularity) were added. Structuring of the terminology content was achieved through specification of relations between term pairs. In this process terms with coarser granularity were used to structure more detailed terms into several hierarchies. In the terminology multiple classification of terms was used when strictly necessary. Only of leaf terms (terms with no descendants) the selectable attribute was set.

In some situations further expressiveness was required, but judged to be only significant for individual cases and beyond the level of relevance that warranted refinement by extension with new (precomposed) terms. In these instances modifiers were added. By associating them with only those terms that they applied to, the need for mechanisms to control the extension process was avoided.

In various parts of the resulting terminology integrity rules were specified. In most instances rules were only included to describe the behavior of the direct children of parent terms, such as their mutual exclusiveness.

Based on the resulting terminology a number of views were defined, representing clinical entities. The construction of views is similar to that of the terminology. However, in our use of the integrity rule and selectable attributes, we followed a different approach. Where integrity rules in the terminology were mainly used to specify the behavior of nearby terms, in views they were also used to implement control that covered much broader ranges of terms. In several places aged and ob-

solete terms were marked non-selectable. Care was taken that these terms were selectable in the underlying terminology, in order to retain the possibility for retrospective coding of historic data. In figure 3.4 part of one of these views, representing the clinical entity "tetralogy of Fallot", is shown.

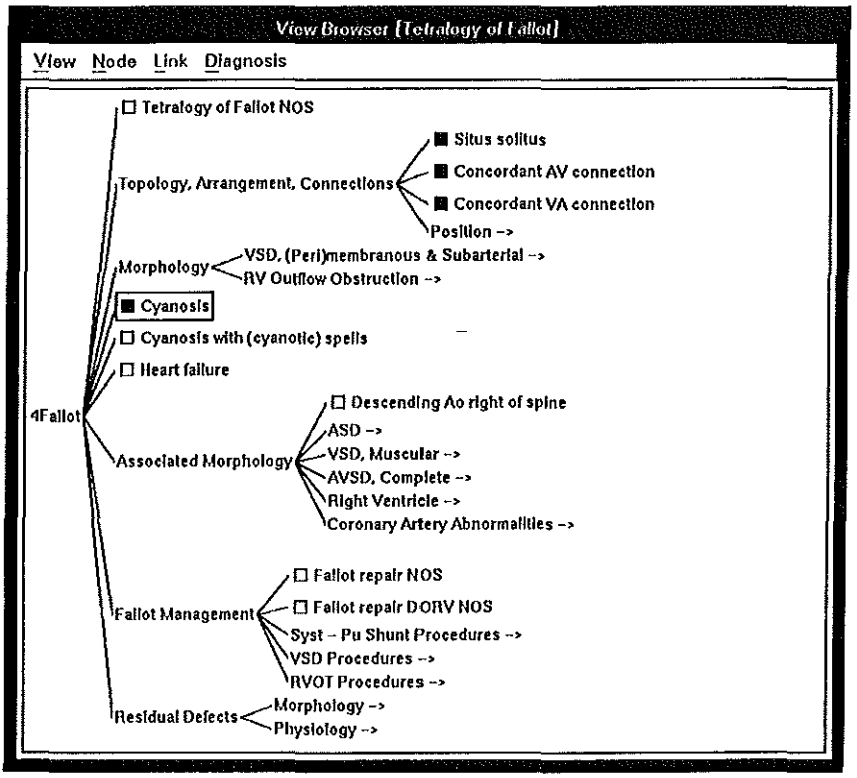

Figure 3.4 : In this figure a terminology view which represents the clinical entity "tetralogy of Fallot" is shown and serves to illustrate the view principle. All nomenclature parts from the underlying congenital heart disease terminology which are relevant to the description of this entity are grouped together. As a consequence this organization of terms differs substantially from the organization found in the underlying terminology. The view is shown in entry mode. There are no term identifiers but buttons have been added when selectable attributes of the respective terms have been set.

To this view a comprehensive collection of almost 60 integrity rules has been added. They enforce correct use of the nomenclature in this view, both at "micro" level, describing combination aspects of nearby child terms, and at more "macro" level, describing the various combinations and associations between larger branches of the Fallot entity.

3.5 Use of the Smart Coding System

User interaction with the SmaCS system, either directly or through a client application, takes place through a graphical interface. This interface has three conceivable states; maintenance, entry, and query mode. Modification of the knowledge base is only possible in the maintenance mode; the other modes are limited to read-only access. In these latter two states maintenance information present in the maintenance mode, such as term identifiers and rule indicators, are replaced by toggles for term selection. In the entry mode, toggles are confined to leaf terms with selectable attributes enabled opposed to the query mode where all terms have toggles.

The maintenance mode provides tools for lexical searches by name, preferred name, synonyms and description attributes of terms. An intelligent "copy" function is present that can be used to duplicate branches of terms into views according to selected SCS relation-types and concept-types, and with or without integrity rules present in the terminology layer. The integrity rule editor contains a parser for evaluation and testing of rules and constraints. Because integrity of the knowledge base is ensured by means of database specific constraints and procedures, no additional functionality was required in the SmaCS system itself. This also guarantees knowledge base integrity when accessed or modified by other means.

3.5.1 Application for data-retrieval

For the extraction of research populations from detailed coded abstractions a query tool was developed. The objective of this tool was to obtain query results by closely approximating the structure of a specific research question. In this approach the various working components of a research query are represented as sets, each set representing a collection of patients based on either a collection of codes or the result of a non code-based query. Essential in this approach is that such a set is a representation of a collection of distinct patients, and not occurrences of a selection criterion. The purpose of a set, especially when it is based on a collection of codes, is to identify the individual patients that meet the clinical aspect represented by the set. A set should not produce the number of occurrences because typically many patients have been attributed several of the codes gathered in the code set.

The final query results are obtained by combining these sets using Boolean logic. Frequently there are several ways in which these sets can be combined and the required research population can be obtained. The query tool also allows inspection of data at various levels, both of individual sets as well as combinations of sets. This gives good insight into and control over the final query outcome as a result of the possibility to monitor the results of individual steps and the effects of modifications. The query tool incorporates facilities for the storage and recall of criteria and results of both individual sets and complete research queries. This permits requerying of the patient database at another moment in time and re-use of individual query components.

Sets which are based on collections of codes are created and modified by making selections in a terminology or view. For this, the terminology system is accessed in retrieval mode. When generic terms are selected in this mode, the hierarchical information in a terminology or view is used for gathering term-codes along all or selected relation-types. In addition to this individual terms or branches can be added or removed selectively. In figure 3.5 the working of the query tool is illustrated.

The query tool has been successfully used for the completion of a number of management studies [3, 45, 46]. The purpose of these studies is development of optimal management strategies for major congenital cardiac entities through evaluation of follow-up patient data.

3.5.2 Application for data-collection

For the purpose of testing integrity rules and to gain insight into the requirements necessary for use of our terminology system in abstraction of patient data, a prototype data-entry tool was developed. Although it has been extensively used for the development and testing of integrity rules, so far, experience with the abstraction of actual patient data is limited.

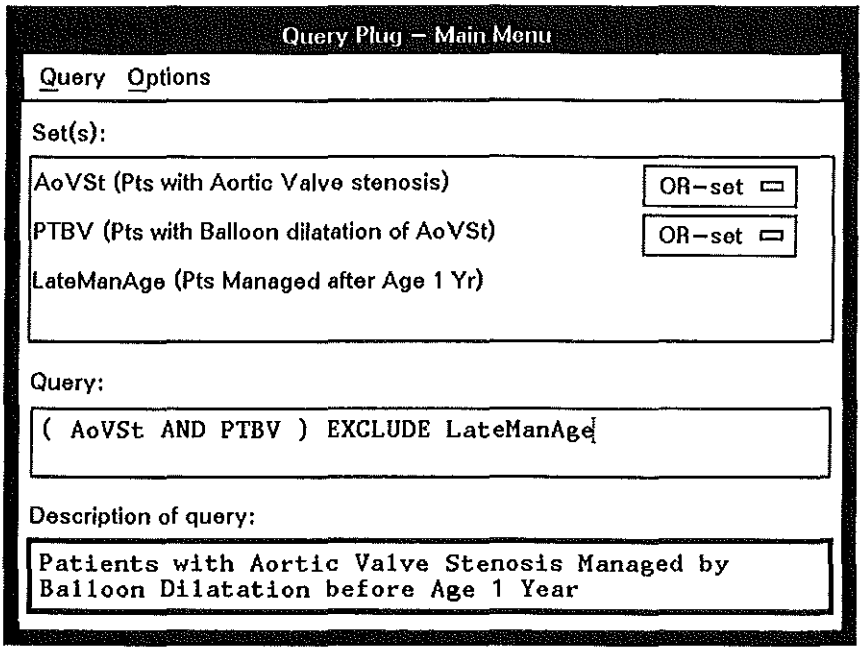

Figure 3.5 : The Query tool that supports stepwise analysis of research queries. In the upper part of the figure, two Code-sets and one Patient-set have been defined. They represent patients with aortic valve stenosis (upper set), patients treated by means of aortic valve balloon dilatation (middle set) and patients that were older than 1 year at the time of intervention. In the middle section of the query tool these sets are combined to give the required study group: patients with aortic valve stenosis managed by balloon dilatation during their first year of life.

3.6 Discussion

Despite the large interest in patient data abstraction and the several projects that aim at development of suitable systems, there are several reasons that justify our approach to the development of "yet another new coding system". In this section these issues will be clarified. One important aspect of our target domain, congenital cardiovascular medicine, is its high level of detail and complexity, but with a relatively small number of main clinical entities. Almost all other coding and terminology systems aim at much broader areas if not general medicine. Our terminology was anticipated to remain small in size.

Our project did not aim at development of an electronic medical record for pediatric cardiology, but a code-based system for controlled coding and analysis of a broad spectrum of time-stamped clinical events. We aimed at abstraction of data specifically collected for medical research, rather than representing and capturing the contents and structure of the medical record in our domain.

It is recognized that such medical record systems that aim at providing sufficient support of the process of care itself have far more elaborate requirements and that the traditional code based systems are insufficient for this [17, 19, 21]. Not only do medical record systems require means for representation of an extensive range of medical concepts to capture the richness, detail, and complicated time-related aspects of clinical information in the medical record adequately. In addition medical record systems also require a formal model of the structure of the medical record that can capture the medical concepts into a record of patient care [6, 47, 48]. Such a model, which has been used as the basis for the PEN&PAD project [28], has been applied in the GALEN project to test the feasibility of this approach [20]. Much of this work is still in the research stage and far from clinical application in computer based medical record systems.

3.6.1 Terminology contents and domain coverage

Congenital cardiology is a highly specialized and complex area of medicine. Patients in this domain cover a broad spectrum in severity and complexity of the underlying cardiovascular abnormalities. The mostly morphological abnormalities range from small and isolated abnormalities to complex disease entities that involve multiple parts of the cardiovascular system. The severity of these abnormalities range from minor not requiring any treatment to life threatening needing immediate intervention. In many instances disease in these patients is not limited to the cardiovascular system; in many patients aspects of pediatric disease or other congenital abnormalities are involved.

Because of this, existing coding schemes such as ICD [49, 50], SNOMED [51], the Read Clinical Codes [52], and the Gabrieli Nomenclature [53] simply do not provide the necessary domain coverage. They do not accommodate the required high level of detail and large areas of nomenclature are generally lacking, especially on surgical and other interventional techniques, complications and electrophysiology. They

also contain outdated or even obsolete nomenclature. Therefore, even combination of these existing large coding schemes to achieve better completeness and domain coverage, as has been done in the UMLS project [31], does not constitute a solution for our terminology contents requirements.

The high level of expressiveness in SNOMED, which is achieved through its capability of constructing missing terms by combining several "atomic" terms (combinatorial extension or postcoordination), in theory could have provided a high degree of coverage and detail. But this would have resulted in a coding scheme with an extreme high proportion of such compound terms with many redundant ones. Rules for the combination of SNOMED terms to form complex concepts are lacking. Efforts are undertaken that apply the conceptual graph formalism to formalize the implicit information in SNOMED terms and to develop these rules to address compositional complexity and redundancy [14, 54, 55].

Finally, a domain specific coding scheme that provided acceptable domain coverage and completeness was already available [34]. Furthermore, use of this scheme also eliminated the need for extensive re-coding of the large follow-up database.

3.6.2 Semantic network approach for terminology structure

Our approach of using a semantic network to structure nomenclature into a terminology is not unique; as was mentioned before semantic networks have been applied by others, such as in the construction Unified Medical Language System (UMLS), and the Medical Entities Dictionary (MED) [13, 31]. However considerable differences exist with respect to aims, terminology content and complexity of the underlying semantic models in these projects.

3.6.2.1 Comparison with other semantic network approaches

Both UMLS and MED are intended to cover far more extensive areas of (bio-) medicine with different aims. The intention of the UMLS is to provide support for access to computerized biomedical information resources. To achieve this in their Metathesaurus the terms (in their approach "concepts") from a number of standard vocabularies are integrated into a network. A Semantic Network is provided, consisting of semantic types and semantic links to classify the concepts and relations of the Metathesaurus. Finally the Information Sources map provides information

on biomedical information resources characterized by means of elements from the Metathesaurus and Semantic Network [31, 56]. The MED has been developed to translate coded information from a number of ancillary systems into a central coding scheme for storage in their clinical information system database [13]. The core of MED consists of a semantic network that was originally based on the semantic types and relations from the UMLS Semantic Network. Terms were taken mainly from ancillary systems and supplemented, when available, with terms from the Metathesaurus. Compared to our project they intend to cover much broader selected medical domains (MED) or even general (bio)medicine, as in the UMLS. As a consequence their terminological contents and underlying semantic models are far more extensive.

An important distinction between the SmaCS and MED approach on the one hand and the UMLS on the other hand relates to the association between terminology contents and underlying semantic model [57]. Although the Metathesaurus concepts are highly interrelated, most of these links are generic broader-narrower links of which only a fraction are related to semantic links in the Semantic Network. This constitutes an important difference with our approach where there is a strict adherence to the fact that each term and inter-term relation in our terminology layer is an instantiation of one concept-type and relation-type in the semantic concept schema; term-pair members linked by the relation are strictly limited to those permitted by the relation-type definition. As a result each relation between terms in our terminology and terminology views represents specific meaning where a substantial amount of the relationships in the Metathesaurus are of the generic "other" character.

3.6.2.2 Significance for terminology creation and use

In none of these projects a similar strict separation between the actual contents of a terminology and their representation has been made. We made this separation based on the assumption that the various tasks involved in the creation and maintenance of a terminology on the one hand and actual use of a terminology for abstraction of medical data (data collection) and analysis of collected data on the other hand all have their (different) optimal organization of terms. The terminology layer is intended as the central resource of a nomenclature and makes it possible to organize terms in a logical organization that is favorable for maintenance,

in our congenital heart disease terminology according to the principles of the sequential analysis. In turn, the views layer provides the means for organizing (parts of) the terminology layer contents in a clinically meaningful way, both for abstraction and analysis of coded patient data. In this way the often substantial differences in optimal nomenclature orientation between these two processes can be met. As such our view mechanisms can be seen as an extension of the notion of "multiple views" in terminologies [21].

The differences between maintenance, abstraction and retrieval are explicit in the three modes in which our terminology system can operate. Only in the maintenance mode one may edit the knowledge base and elementary tools for its maintenance and extension are provided. The main differences between the entry and query modes are the possibility for gathering detailed terms into broader medical concepts (query mode) and activation of the rule mechanism (entry mode). Also in entry mode the selection of terms is limited to those that have their selectable attribute set. The differences in graphical presentation between the three modes are minimal providing a consistent "health care worker friendly" environment for the use of terminologies.

The rapid evolution of clinical care, which is especially prominent in congenital cardiology, makes maintenance and extension of terminologies indispensable. When terminologies are large, maintenance by human effort alone is no longer feasible. Knowledge-based tools have been developed to support these tasks [13]. Maintenance tools could be kept simple, because the size of our congenital heart disease terminology is small compared to other systems and is anticipated to remain manageable (not exceeding 5000 terms in the near future).

Using the semantic network principles we were able to build a terminology system and develop a prototype terminology on congenital cardiology that meets the requirements described in section 3.2 of Chapter 2. It is domain complete, maintainable, has multiple classification of terms, provides different levels of granularity, and accommodates explicit relationships between terms. As a result its contents are unambiguous, non-redundant and synonyms are provided in many situations [21]. We argue that a clinical representation approach which enables organization of nomenclature in a manner that closely approaches the clinical context it is used in,

whether for data collection or analysis of patient data, is essential for successful use of "systematized" coding and terminology schemes. Also storage of data in their explicit context is recognized as an important requirement for correct retrieval and interpretation [42, 43].

3.6.3 Knowledge representation for completeness and correctness

In our approach the rule mechanism enables specification of explicit control at the level of individual terms. This introduces a type of control that is much more detailed when compared to rules and procedures specified at more generic levels controlling combinatorial aspects of classes of terms in stead of individual terms. When a given set of terms is used more than once in several different views, rules specified for this term set may differ from view to view. In these cases the rules operate independently from each other and supersede the rules for these terms in the terminology layer when present. This enables control over term selection within the context that is represented in a view. In this way the value and importance of a given set of terms or individual terms may differ among several contexts, and thus may require different rules, although in themselves these terms have unambiguous meaning.

The concept of including rules and procedures in terminology schemes has been utilized by others but with different aims. Others have used rules and procedures for purposes such as control of combinatorial extension or the use of modifiers. An example is version 3.1 of the Read Clinical Codes [52] in which modifiers were introduced together with a collection of "rules", in their system called templates, that were added to control the process of combining these modifiers with terms. Although modifiers can be introduced in our system, rules to control the extension of terms with these modifiers are not required as a result of the manner in which they are implemented. Modifiers in our system are specified as attribute values of individual terms. Consequently, they only apply to those terms to which they have been linked.

A far more extensive use of rules and constraints is found in the GALEN project [20]. The GALEN project aims at providing a comprehensive model of medical concepts, the COding REference (CORE) model. In this project comprehensiveness is achieved through creation of complex medical concepts by means of composition

out of simpler ones. This composition process allows creation of concepts of unlimited complexity but it requires a complex and extensive mechanism of rules and constraints to achieve proper control. Although it has been recognized that realization of this is a massive task it is argued to be feasible [29]. Their rules and constraints operate at a different level; they control a recursive combinatorial extension process. Because our terminology almost exclusively consists of compound terms, such a type of control is not needed. Our rules are intended for specification of associations between terms or groups of terms within and across terminology branches.

3.7 Limitations and future work

Although the integrity rule mechanism allows a high level of control over the term combination process, a number of limitations have emerged. Implementation of rules is a labor intensive process. Because many rules relate to the direct descendants of a parent term and in many instances have a limited range of structure such as mutual exclusiveness, generalization of such rules as predefined integrity rule attribute values is preferable. In some situations the Boolean nature of rules was found to be too strict. Extension of functionality with an uncertainty operator that allows specification of (im)probable but not (in)correct combinations of terms would greatly enhance functionality of the rule mechanism.

We anticipate that about 50 clinical entities, implemented as views, will be required for abstraction of the majority of patients with congenital cardiac defects. Full realization of this view definition will involve substantial effort from congenital cardiac specialists and cardiothoracic surgeons. In addition, the congenital heart disease terminology is being modified and extended to incorporate nomenclature from other domain specific and more general vocabularies to enable inter-terminology translation. This will enable analysis of patient data gathered with other abstraction systems.

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Coding of complex congenital heart disease

4

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4.1 Introduction

Since the introduction of the segmental analysis by Van Praagh et al. [1-3], the structured description of congenital heart disease morphology has been an active field of research. Over time important changes in the approach to the description of congenital cardiac abnormalities have been introduced. Among these changes, the notion of a more sequential approach and a shift of emphasis towards description of connections between the heart components (intersegmental description) in addition to describing the components themselves (intrasegmental description) are the most important [4-6]. Since then the general principles underlying the sequential segmental analysis have remained unchanged although small modifications have been introduced to enable description of specific and rare cases [7].

At various stages in this development enumerated coding schemes were developed to facilitate (computerized) storage and identification of individual cases [8-10]. However, none of these schemes acquired general acceptance as a standard and with one exception [11], all of these schemes were paper-based when published.

In this paper we describe the development of a (computerized) system for the management and use of a medical terminology applied to congenital cardiology and its associated domains. Nomenclature for the description of patients with Fallot's

tetralogy is used to illustrate the various aspects involved in the maintenance and especially the clinical use of a complex specialized nomenclature.

Our work aims at development and application of methodology for the collection and analysis of complex and detailed follow-up and management data in congenital cardiology. In this paper, it is not our purpose to cover all aspects of the diagnosis, management and follow-up of patients with tetralogy of Fallot. This disease entity serves an illustrative purpose; therefore the nomenclature used in the Figures is not exhaustive and has been simplified for clarity in several places.

4.2 Methods

4.2.1 Background

Research on morphogenesis and development of accurate methods for the description of congenital cardiac malformations has been and still is an active field of research. In the early sixties Van Praagh and co-workers introduced the concept of the segmental analysis [1, 2]. The foundations of current descriptional methods are rooted in this work. Since its introduction, the segmental approach has undergone numerous changes, substantial and minor. The most important of these was the introduction of a variant of the segmental analysis, the sequential segmental approach by a group of morphologists based in the United Kingdom [4-6]. In this approach emphasis is put on the connexions between the cardiac segments rather than on the segments themselves. Since then the two methodologies have evolved separately, though not independently.

In parallel with these developments several coding schemes were introduced in which individual items ("terms") of congenital heart disease nomenclature were recognized and identified by means of a code. Such coding schemes, either developed new [8-10] or as extensions of existing generic ones [12], served to label patients with congenital cardiac abnormalities. Although intended to provide a standardized and unambiguous method to facilitate storage and retrieval of patients for administrative, statistical and research purposes, none of these schemes has gained universal acceptance. The main reasons for this were related to limitations in their content and structure. Contents were usually based on insights current at the time the

scheme was developed and which usually reflected one of the two morphologic approaches. In most schemes only morphologic aspects were included and terms for description of additional abnormalities and follow-up events such as treatment, complications and residual defects were usually not or only partially incorporated. Their structure, usually based on principles of anatomy with terms organized into tree like hierarchies, proved unsuitable for clinically oriented use. Together with lacking control over the process of translating patient data into coded form (data "abstraction") in terms of correctness and completeness this task of abstracting patient data was error prone.

Experiences with coding schemes in congenital cardiology, other specialties and in general medicine, have indeed shown their limited suitability for (computer-based) collection and manipulation of coded patient data [13-15]. These experiences and the recent increasing interest in the development of computer-based patient records, in which suitable abstraction systems are a key component, have intensified research in medical informatics. An important insight that evolved from these efforts is that such systems ("terminologies") require a more advanced organizational structure than the traditional hierarchical coding schemes which are simple lists ("vocabularies" or "glossaries") with little underlying structure. Currently there is consensus that an advanced coding system should also contain formalized domain specific (medical) knowledge [16-20]. Several approaches to the representation of knowledge, mostly originating in computer science, have been adapted by workers in medical informatics for such representation of domain specific medical knowledge in data abstraction systems. One such approach is the use of semantic networks [21, 22].

4.2.2 Modeling domain knowledge on congenital heart disease

4.2.2.1 Semantic network approach

We applied a semantic network approach for the realization of our terminology system. In such an approach the individual items of a nomenclature are structured in a meaningful way by means of links that connect individual terms with each other. These links, "relations" represent some aspect of the relationship that is present between the members of the term pair. Actually, such a relationship constitutes an aspect of (implicit) domain knowledge that is made explicit, "formalized". For example, the terms "Atrial septum" and "Secundum type atrial septal defect"

are linked through a relation with the character "Has Abnormality". Terms may participate in multiple relationships that do not necessarily need to have the same character. Relations also have a direction; they start in a "parent" term and end in a "child" term. A semantic network property is that several parent terms may be related to the same child term. As a consequence the resulting structural organization is not strictly hierarchical but has the form of a network. Also, such a network may have several entry points with each entry point giving rise to a different view on (parts of) the terminology contents.

4.2.2.2 Semantic network representation based on concepts

Terms in a nomenclature are the "units of language" that collectively describe selected aspects of a (medical) domain. As such, these terms are not sheer parts but can be regarded as examples of more abstract "units of thought" or concepts. In our terminology system, such concepts can be specified as concept-types. For example, the terms "Ventricular septum", "Aortic valve", and "Non-coronary cusp" can be regarded as instances of the concept-type "Cardiac component". Likewise "Ventricular septal defect" represents an instance of the concept-type "Abnormality". In such a way the contents of a nomenclature can be represented by a limited collection of such concept-types. Characteristics of individual terms, such as their name, associated code, or synonyms can also be abstracted and represented as the "attributes" of a concept-type. In a similar way the relations between terms can be regarded as instances of "relation-types"; the characteristics of relations formalized as attributes of the relation-types. One aspect of relations that is formalized in these relation-type attributes are the concept-types from which the terms connected by a relation are instantiated. For each relation-type a starting and ending concept-type is needed and gives the relation-type a direction. These two "semantic attributes" may refer to either a single or to different concept-types. Between the terms "Aortic valve" and "Non-coronary cusp", both instances of the "Cardiac component" concept-type, a relation is present that is an instance of the relation-type "Has sub-component". Both semantic attributes of this relation-type refer to the same concept-type and therefore its instances represent a "broader-narrower" or "specialization" relationship between the terms it connects. When the semantic attributes refer to different concept-types a relation-type ensues that is illustrated by the "Has abnormality" relation between the terms "Ventricular septum" and "Ventricular septal defect". In figure 4.1 the principles of concept-types,

relation-types, terms, relations and their role in the formation of a semantic network are illustrated.

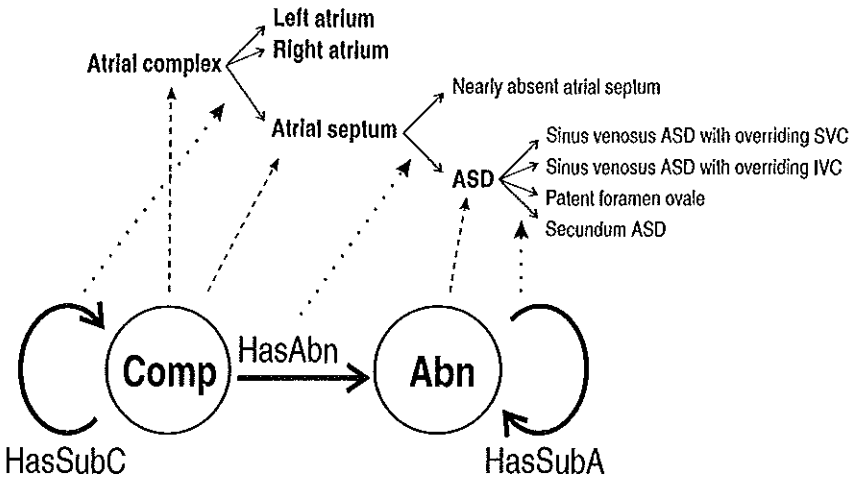

Figure 4.1 : In this figure a number of principles of nomenclature representation and structuring of nomenclature elements in a semantic network are illustrated. Circles and thick arrows represent concept-types and relation-types respectively. Words in the upper part of the figure are terms instantiated from concept-types shown in the lower part of the figure. In a similar way, the relations that connect these terms are instantiated from the relation-types. These relations are shown as thin solid arrows. The instantiation process is indication by means of the dotted arrows. Comp = Cardiac component, Abn = Abnormality, HasAbn = Has abnormality, HasSubC = Has sub-component, HasSubA = Has sub-abnormality.

These concept-types and relation-types together constitute a formal model, also called an ontology, that serves as a framework for storage of both the nomenclature terms as well as domain specific medical knowledge. This knowledge not only describes aspects of the individual terms but is also used for the formalization of "higher" and more complex aspects. For example, the inter relationships between the heart components, the spectrum of abnormalities that can be found in these abnormalities as well as their physiologic consequences and the treatment options that are available.

4.2.2.3 *Views and clinical entities*

Also the fundamental differences in approach to a common medical domain that exist between different specialties can be made explicit. For example, the (cardiac) morphologist prefers an organization of nomenclature according to principles of anatomy, whereas the congenital cardiologist favors representation based on clinical entities, such as Fallot's tetralogy, in which only nomenclature parts relevant in the clinical entity, that may be widely separated in the morphologists "view", are grouped together. Both approaches or "views" use the same "basic" terminology; they differ in the subset of terms they use from the basic terminology, their entry point in the semantic network, and the relation-types that are used to arrange the subset terms. This principle is illustrated in figure 4.2. Whenever a term from the basic terminology is used in one or more views, some of its attributes are extended with "copies" that replace some of the basic terminology attributes of the term in each view. This makes it possible to specify different or modified values for some of the term attributes that are specific to the view in which the term is used.

4.2.2.4 *Combinatorial knowledge*

A final aspect of knowledge deals with the combinatorial aspects among the terms in branches of terminology network. For example, the terms "ASD closure by direct suture", "ASD closure using patch", and "Transluminal ASD closure with device" are the direct descendants or "children" of the term "ASD closure". When describing an ASD treatment event in a patient, this consists of just one of these three options as they are mutually exclusive. This aspect can be formalized by means of an "integrity rule" specified at the level of the "ASD closure" term. Based on the same principle complex rules can be implemented at various levels in an hierarchy. In the aforementioned Fallot's tetralogy view for example, they can be applied to enforce that correct coding of morphology is a prerequisite for coding a management intervention or that postoperative complications can occur only in the presence of an intervention.

In our approach such a rule consists of a combination of term identifiers and logical functions that evaluate to either "false" or "true", depending on whether a valid combination of selected terms is made. Rules are stored as one of the term's attributes.

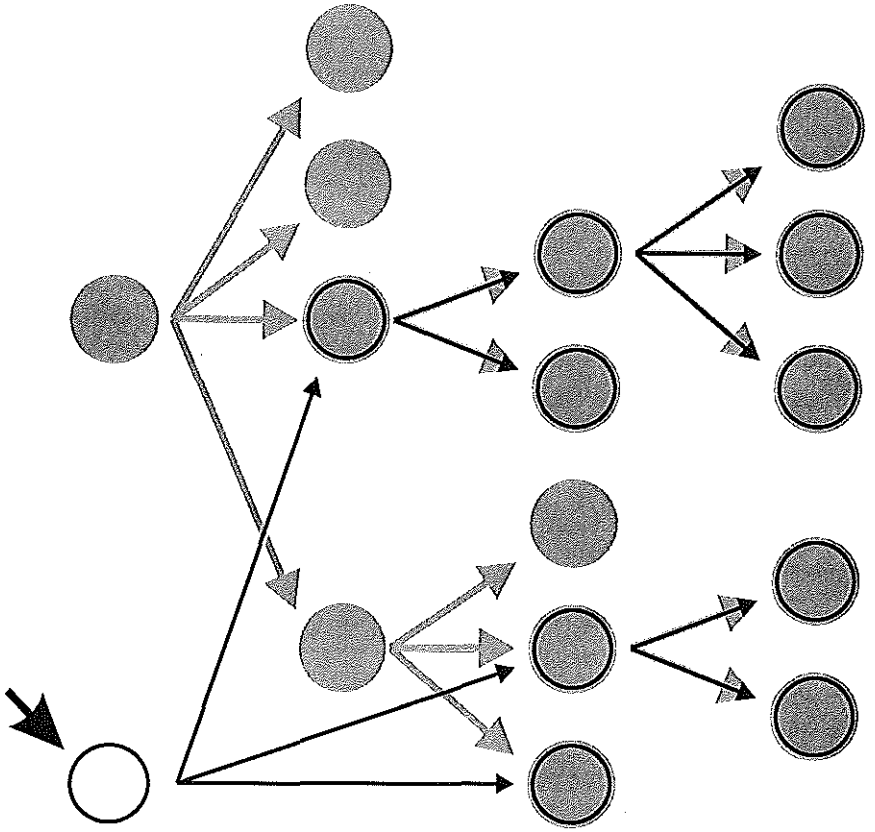

Figure 4.2 : Illustration of differences in terminology organization that result from choosing different entry points in the terminology. A basic terminology structure is shown, represented by grey arrows and solid grey circles. Such a structure can be based on principles of anatomy, for example, by means of which a systematic organization is realized that is favorable for maintenance and extension. The arrow in the lower part represents an alternative entry-point in the terminology hierarchy. Following the thin black arrows, that represent alternative relations, a "view" on the underlying basic terminology is achieved. Such a view can be used to represent a clinical entity in which, by means of its view relations, only terminology parts relevant in the context of this entity are gathered.

4.2.3 Terminology system design

From a functional point of view our system is based on two main components. There is a central resource, or "knowledge base", that stores both the nomenclature elements and the formalized domain knowledge. The second component is the software system that is necessary for construction and maintenance of the knowl-

edge base and enables the use of its contents to support patient data abstraction, storage and successive retrieval. In figure 4.3 a schematic overview of the terminology system is shown. In the figure caption a more detailed description is given of the knowledge base structure and the system components. A more technical description of the system is presented elsewhere [23, 24] and in Chapter 3.

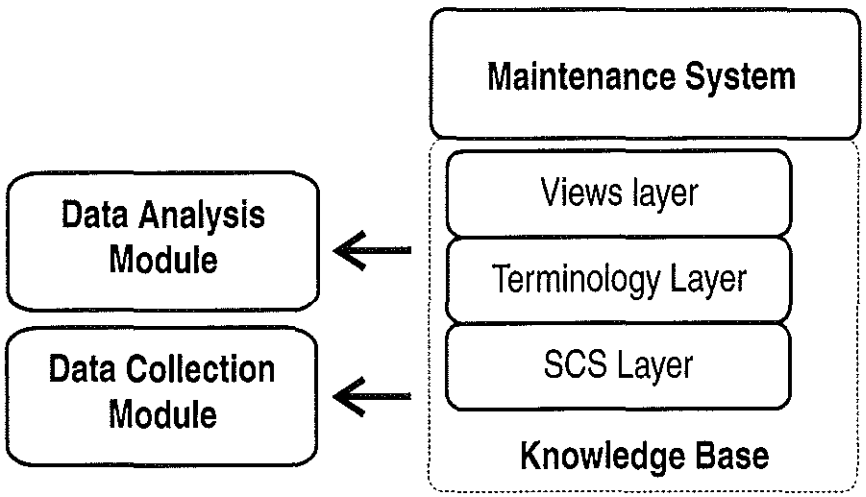

Figure 4.3 : Schematic overview of the Smart Classification System (SmaCS). In the right the main components of this terminology system are shown; the knowledge base (lower part) and the maintenance system (upper part). The knowledge base itself has a layered structure. Each layer contains specific aspects of the terminologies that are stored in this knowledge base. The Semantic Concept Schema layer (SCS layer) contains the model of concept-types and relation-types on which a terminology is based. Based on this model all nomenclature elements in a terminology are organized in several hierarchies through specification of inter-term relationships. The Views layer contains alternative organizations of nomenclature subsets. The contents of these subsets are based on the contents of the underlying Terminology layer. The relations present in the Views layer need not be present in the Terminology layer, as long as they meet the relation-type definitions in the SCS layer.

The left part of the figure shows two additional system components; the "Data Collection" and "Data Analysis" modules. These modules serve to support collection and analysis of coded patient data respectively. They use the terminology system as a resource for the codes used in collection and analysis.

4.3 Results

4.3.1 Aspects of terminology contents

Based on an existing vocabulary on congenital cardiac nomenclature [11] a new terminology was developed. In its latest version this coding scheme contained about 3800 terms. The main reasons for using this original code were the relative complete coverage of the congenital heart disease domain this code provided and the vast amount of valuable consecutive patient data that have been collected with this vocabulary over the last 6 years.

In a collaborative effort by workers from the pediatric cardiology and medical informatics domain this vocabulary was modified and extended at length. Because the old code only contained leaf terms, i.e. terms available for selection, many generic ones were introduced for structuring these leaf terms into hierarchies. Where needed branches were extended or modified to implement new insights or management techniques. In all this maintaining compatibility with historic coded data was fundamental. To acquire a high degree of maintainability, a systematic anatomic organization similar to the sequential segmental analysis was used.

4.3.1.1 Clinical approach to terminology use

One aspect of prime importance when abstracting patient data into coded form is that the terminology system used for this process is capable of representing coding options in a way that closely reflects the clinical context from which the data originated. Within the congenital cardiac domain a substantial fraction of patients present with abnormalities that can be categorized as one of a limited spectrum of combined lesions; "congenital cardiac entities". Within such an entity, of which tetralogy of Fallot is an example, there is a limited spectrum of relevant structural, management, and follow-up aspects. Using such implicit "knowledge" to control terminology presentation, an organization of terms is achieved that closely resembles clinical practice and is limited to those aspects that are relevant in the context of the presented entity. Based on the systematic terminology, several views for the representation of such congenital cardiac entities were created. Many aspects of both terminologies and their views are illustrated in figure 4.4 which shows part of a view on nomenclature involved in the coding of patients with Fallot's tetralogy.

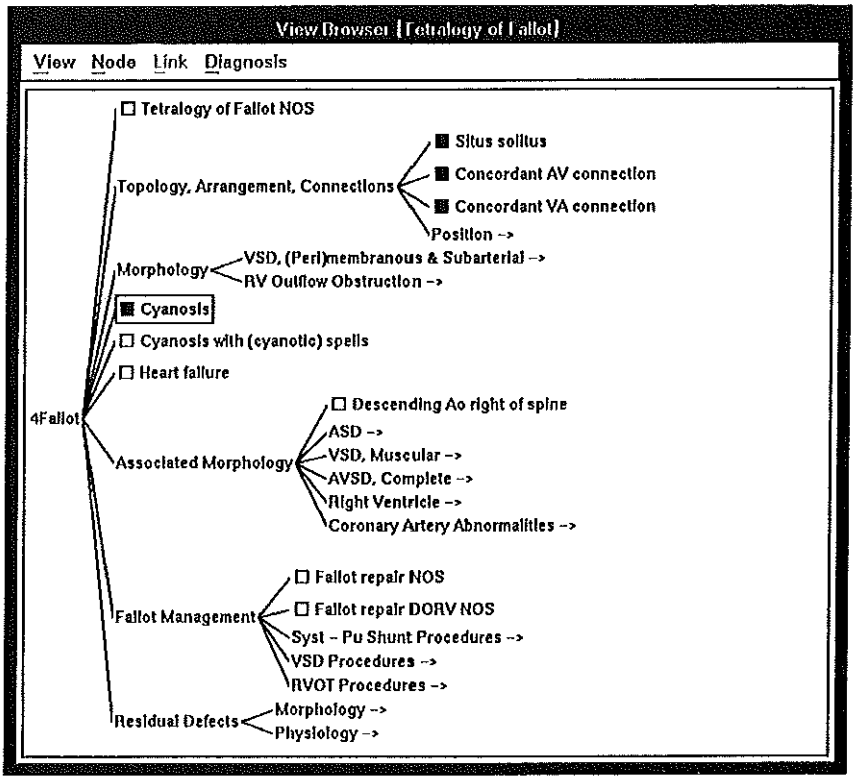

Figure 4.4 : In this figure a view is shown of nomenclature used in the clinical entity "Tetralogy of Fallot". Description of this figure will focus on three aspects; its syntax (which elements can be seen in the figure), its semantic meaning (what do these elements represent), and aspects pragmatics (how are these elements used).

In this figure several nomenclature elements (terms) used in the description of patients with Tetralogy of Fallot are presented in a graphical manner. Individual nomenclature elements are organized in a hierarchy by means of relations that link individual terms. From left to right the level of detail of terms increases. Two types of terms can be discerned; leaf terms for which there are no further specializations and branch or generalizing terms. The terms "Tetralogy of Fallot NOS" and "Topology, Arrangement, Connections" are examples of leaf and branch terms respectively. In the figure only 3 levels of detail are shown. When further specializations of a term are available this is indicated by an arrow at the end of a branch term. Relations between terms represent a meaningful (medical) aspect of the relationship between term-pair elements. For example the terms "Cyanosis", "Cyanosis with (cyanotic) spells", and "Heart failure" are related to the term "4Fallot" by means of an "Has Symptom" relationship.

The figure as a whole illustrates the view concept for the representation of a clinical entity, such as Tetralogy of Fallot. In a view all terms that are relevant to the description of an entity are grouped together. These

terms are always a subset of the terms present in the terminology a view is based upon, but are organized in a way that may differ substantially from the organization used in the underlying terminology. For example, in the branch "Morphology" two separate branches are assembled; "VSD, (peri)membranous & Subarterial" and "RV Outflow Obstruction". In the underlying terminology these two branches are widely separated. Furthermore, the "VSD, (peri)membranous & Subarterial" branch is a stripped down version of the "Ventricular Septal Defect" terminology branch; the section on muscular VSD nomenclature has been left out. In contrast with the subset requirement for the terms in a view, the relationships in a view do not have to be present in the terminology. This is also illustrated in the "Morphology" branch. The two relations that link the "VSD, (peri)membranous & Subarterial" and "RV Outflow Obstruction" are not present in the terminology; they are only present in this view. Even relationships may be specified that are of a relation-type that is not used for relations in the terminology, as long as this relation-type is present in the Semantic Concept Schema the terminology and its views are based upon.

In this figure the view is presented in data-entry mode which is characterized by the presence of selection buttons in front of those leaf terms that are enabled for selection. "Cyanosis" and "Situs solitus" are examples of terms that have been selected. Although a clear distinction has been made between a terminology and its views from a technical, conceptual point of view; visually they present in a similar way. What is not visible in this figure but constitutes an important aspect of especially terminology views are the integrity rules. In the tetralogy of Fallot view these rules, almost 60 in number, have been introduced to enforce correct use of the individual view terms. For example a rule which is present at the "Morphology" term specifies that in a complete description of a patient with tetralogy of Fallot the combination of a ventricular septal defect (of perimembranous or subarterial morphology) and some form of right ventricular outflow tract obstruction is obligatory. Those morphologic abnormalities that are not essential in this entity but may co-occur, such as muscular VSD's or aberrant coronary arteries, are grouped in a separate branch. To guard their co-occurring nature, the rule specified at the term "Associated Morphology" checks that in case selections have been made among its "child" terms this is balanced by a valid description of the VSD and RV outflow tract obstruction in the "Morphology" branch.

4.3.1.2 Domain completeness and management of terminology

Within each domain of medicine nomenclature is constantly changing and extending. This is especially prominent in congenital cardiology. Not only have contents of and approach to the description of morphology changed substantially over the last decades; new and improved management techniques are introduced constantly. As a direct consequence of this, keeping a terminology up-to-date has become essential. This does not only involve extension of a terminology with improved or new terms but also correct handling of terms that have become obsolete, because elimination of such terms would violate of the integrity of historic data.

In our approach obsolete terms can be tagged, by means of their attributes, in such a way that within a view such terms are no longer "selectable" while retaining

them for research purposes. Figure 4.5 shows a branch from the management section in the tetralogy of Fallot view. Palliation with a systemic to pulmonary shunt is currently almost exclusively realized by means of the modified Blalock interposition. Historically this technique was preceded by several other approaches such as the classical Blalock anastomosis, the Waterson, and Pott's anastomoses. These terms are present but not available for selection in this view. Because in the underlying terminology they have not been tagged "non-selectable" they do remain available for (retrospective) coding of historic patient data and for use in unusual situations.

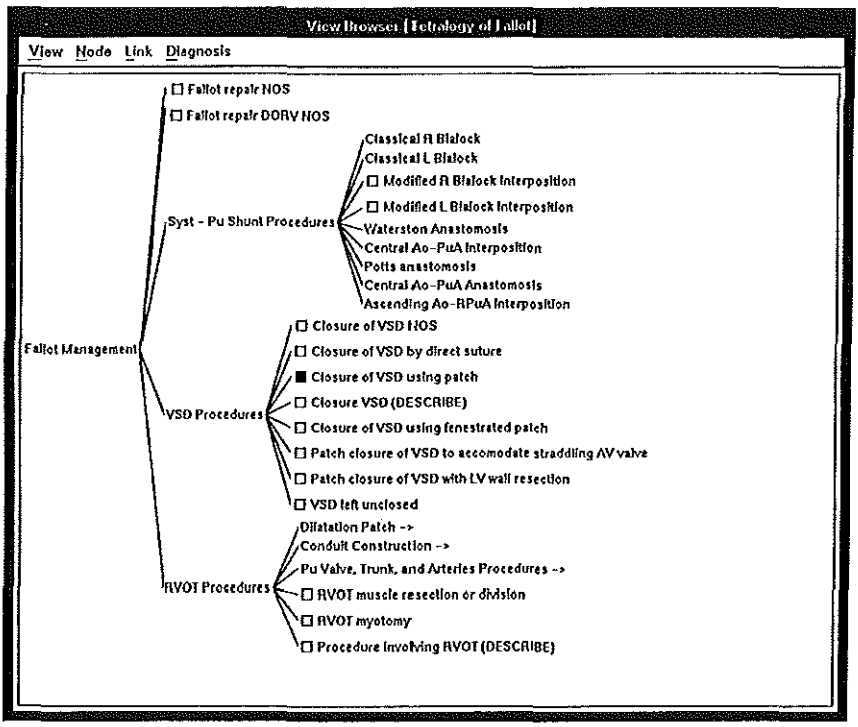

Figure 4.5 : The branch of the Fallot's tetralogy view from figure 4.4 representing options for coding of Fallot management. Essential in this branch is the absence of selection buttons for old (palliative) procedures for the creation of systemic to pulmonary shunts.

When coding a management event for a given patient, this consists of either a palliative procedure or surgical correction of the underlying lesion. Whereas the palliative approach involves the creation of a systemic to pulmonary shunt, surgical correction consists of release of the right ventricular outflow tract obstruction and closure of the VSD. In the figure, at the level of the term "Fallot Management", these combinatorial

aspects are enforced by means of an integrity rule. This rule has been specified as: M1324 XOR (M1204 AND M1693). The numbers preceded by the character "M" are term identifiers: "Syst - Pu Shunt Procedures" (M1324), "VSD Procedures" (M1204), and "RVOT Procedures" (M1693). "XOR" and "AND" are logical functions. Term identifiers obtain a logical value, either "False" or "True" whenever one or more of their children are selected and integrity rules specified for their children are evaluated. For example the branch term "VSD Procedure" has become "True" because the term "Closure of VSD by direct suture" has been selected. Whenever the person performing the coding indicates to the system that coding has been completed, integrity rules are checked. In the example rule it is checked whether either a shunt procedure was coded or a VSD procedure in combination with a RVOT procedure was specified. Whenever the most generic rule, i.e. the rule at the least detailed level, evaluates "False", the coding is invalid and a message is displayed. In the figure the coding is invalid because only a VSD procedure has been specified, lacking description of the obligatory RVOT procedure.

4.3.1.3 Integrity of abstracted patient data

Correct use of nomenclature for patient description is promoted in our terminology system by means of inter-term relationships that link rational terminology parts and presentation of relevant terminology parts in views. Although such explicitations facilitate correct use of terms to a large extent, they do not enforce or check this. Many erroneous, missing, and contradictory information in abstracted data are the result of so called "random errors" such as typing mistakes or other forms of human error. These undeliberate inconsistencies are important in that they may reduce the usefulness and validity of collected patient data, especially when used for research purposes.

We used a rule mechanism to achieve further control over the completeness and correctness of abstracted data. These rules are associated with individual terms and are a combination of term identifiers and logical functions. Rules evaluate to either "true" or "false" depending on the combination of selected (or non-selected) terms that has been made. Many of such rules are present in the tetralogy of Fallot entity shown in figure 4.4. Example rules are described in the caption of figure 4.5 to illustrate the principle.

4.3.2 Analysis of patient data

Collection and analysis of patient data are inherently different processes. The former is patient oriented, requiring detailed items for abstraction; the latter is group oriented; focused on more generic (less detailed) criteria. Also the context of a re-

search query may differ from the context used for abstraction of patient data; e.g. in many situations a specific management approach or specific residual defects are the starting point. Essential for identification of research populations based on less detailed criteria is grouping of relevant detailed terms into more generic ones. Inter-term relationships can be used to gather specializing terms into the required term collections.

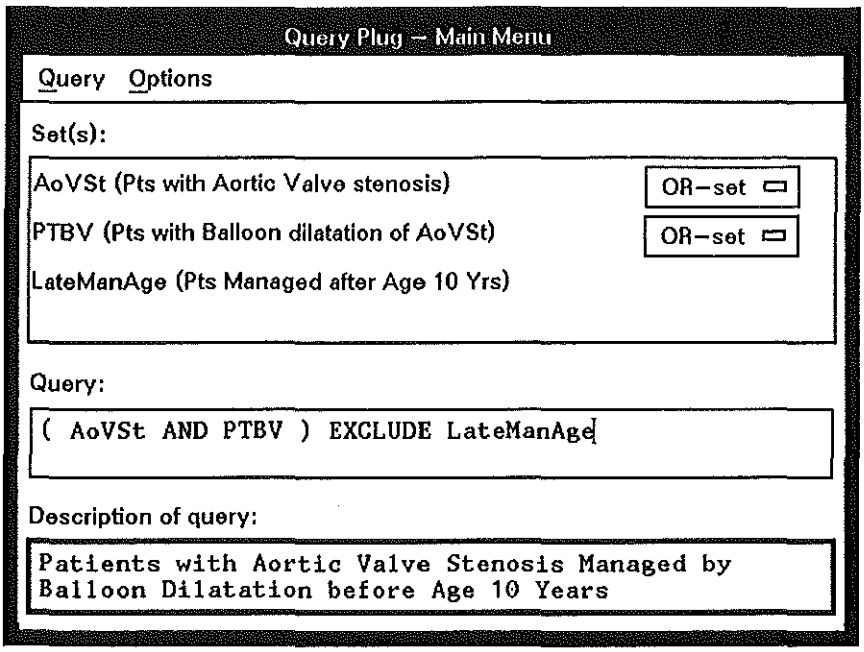

Figure 4.6 : Illustration of the use of a module that supports stepwise analysis of research queries. In the upper part of this figure, two "Code-sets" and one "Patient-set" have been constructed. Code-sets are based on collections of codes gathered from a terminology or its views by means of the terminology system. They represent a collection of patients that have one or more codings present in the code-set. In the example code-sets represent patients with valvular aortic stenosis and patients managed by balloon aortic valvuloplasty respectively. In the central part of the figure these sets are combined by means of logic. The result is an intersection which contains patients with aortic valve stenosis that underwent valvuloplasty. This patient group is further restricted by excluding patients managed after the age of ten years. These patients are represented in a Patient-set which is based on age at intervention.

Identification of research groups is a step-wise process. We have developed an approach in which a specific research question can be solved by combination of

the elementary components of a question using logical functions. Each component consists of either a set codes that represent a group of patients or a set of patient identifiers obtained by other means than selection based on diagnostic codings. In figure 4.6 the retrieval module is used to illustrate how it works.

4.4 Discussion

In comparison to the other coding schemes that were developed for coding of data on patients with congenital cardiac abnormalities [8, 10] our terminology is more complete. In existing schemes especially areas on treatment, complications and residual defects are limited or absent. With respect to structuring of nomenclature, we focused on organizing nomenclature in such a way that the synthesis between morphologic, physiologic, management, and outcome aspects of congenital cardiac abnormalities become evident. This systematic, though still sequential, organization of nomenclature was further extended by grouping relevant terminology parts into clinical congenital heart disease entities. Other coding schemes adhere strictly to anatomy for their organization.

In addition to medical domain knowledge for the structuring of nomenclature, we introduced the concept of explicit control over combinatorial aspects of nomenclature to improve completeness and correctness of collected patient data. Weinberger stressed the importance of using clinical entities as a starting point for the description of congenital heart abnormalities [8]. However, in his approach they are merely a list of bypass codes and the implicit knowledge contained in these entities is not used to explicitly control the presentation and use of a nomenclature. Because the terminology system presents nomenclature in its clinical context, it is also valuable for teaching purposes because the relationships between morphology, physiology, and options for management are made clear.

In medical informatics, substantial research effort is directed toward development of intelligent knowledge-based terminologies and coding schemes [20-22]. Our project differs from these other approaches in several ways. We focus on a highly specialized domain, congenital cardiology, where others focus on broader areas [22] or general medicine [20, 21]. Also there are differences in aim. Translation between different

nomenclatures and support of access to biomedical information resources that utilize different nomenclatures [21, 22], or structuring of (medical) language as it is found in the paper-based medical record [19, 20, 25]. Also, none of these approaches contain our notion of views to achieve flexible, clinically oriented representation of terminology and rules to control collection of patient data to improve its quality. Also the system was specifically designed to support both the data collection and the retrieval process, using a central maintainable terminology.

For research purposes the quality of data is of prime importance. Several studies have shown that data collected using more "traditional" coding schemes, such as the ICD [26] and SNOMED [27], contain many errors and inconsistencies and as a consequence have reduced value for research [28-30]. Therefore we argue that a maintainable, flexible, controlled and clinically oriented representation of nomenclature is of major value to acquire accurate, high quality patient data and to support subsequent retrieval for research.

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Part 2
Clinical management studies

Morphological, haemodynamic, and clinical variables as predictors for management of isolated ventricular septal defect

5

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5.1 Abstract

Objective: to assess the predictive impact of morphological, haemodynamic, and clinical variables in the management of patients with isolated ventricular septal defect in a retrospective analysis of variables by a sophisticated database management system.

Patients and methods: 263 consecutive patients with isolated ventricular septal defect diagnosed by echocardiography. The morphological type and haemodynamic character of the ventricular septal defect was characterised in each patient. In addition, variables were introduced to represent the need for diuretics, growth and potential delay in growth. In 43 patients (16.3%) the ventricular septal defect was closed surgically; 220 patients (83.7%) were managed conservatively and spontaneous closure of the ventricular septal occured in 65 (29.5%) patients. There were no deaths.

Results: all patients managed surgically had non-restrictive defects and were operated on during the first year of life. A few patients with non-restrictive defects were managed conservatively. The two groups differed significantly only with respect to mean growth delay (0.65 (0.27) vs 0.9 (0.21), $p < 0.001$). Only the morphology of the ventricular septal defect significantly ($p < 0.001$) influenced the probability of closure.

Conclusions: findings imply that early surgical closure of ventricular septal defect is indicated in patients with non-restrictive ventricular septal defect and severe growth-delay. Other patients should be managed conservatively. In these patients the morphologic type of the defect determines the probability of spontaneous closure and provides an estimate of the period over which decrease in size or closure can be expected.

5.2 Introduction

Non-restrictive ventricular septal defect giving rise to cardiac failure is generally accepted as an indication for surgery. The timing of surgery, however, is still controversial mainly because of the risks of developing pulmonary vascular obstructive disease and the probability of spontaneous closure of the defect [1-3]. Other influences are local experience with early primary repair and the infrastructure for post-operative care [1, 4].

Only a minority of patients with isolated ventricular septal defect will ultimately require surgical intervention. Such defects tend to close spontaneously. In several studies the morphologic type of the defects has been identified as the most important determinant of spontaneous closure [2, 5]. Although there is consensus on these qualitative aspects, quantitative insight into the probability of closure over time is generally lacking.

To gain more insight into the variables that determine the management of patients with isolated ventricular septal defect we studied retrospectively a series of 263 such patients. We identified variables that may have determined or influenced the observed treatment, and we assessed the natural course of ventricular septal defect in relation to its morphological type and size in patients who were managed conservatively.

5.3 Patients and methods

5.3.1 Patients

We studied 263 consecutive patients born between 1 January 1989 and 1 September 1993, who were diagnosed as having an isolated ventricular septal defect at this hospital. Only patients with isolated ventricular septal defect or ventricular septal defect in combination with an open foramen ovale were included in the study. Patients with additional structural cardiac abnormalities were excluded. All cases were diagnosed by echocardiography. In some patients additional information obtained by cardiac catheterisation was available.

One hundred and twenty seven patients were girls and 136 boys. Mean age at diagnosis was 2.9 months (range 0 to 30 months). Mean duration of follow-up was 15.5 months (range 1 month to 4.3 years).

All data were collected using a dedicated pediatric cardiology database management system on a personal computer (RW Brower, unpublished data). Both diagnostic and management data were coded with an extensive classification system based on sequential analysis [6].

5.3.2 Characterisation of defects

Ventricular septal defects were classified as muscular (n = 105), perimembranous (n = 95), perimembranous with extension to either inlet or outlet parts of the interventricular septum (n = 36), or subarterial (n = 4). In 23 patients the ventricular septal defect was characterized as small with no other details. To measure the hemodynamic importance of the ventricular septal defect each defect was characterized as either restrictive or non-restrictive according to Doppler echocardiographic data or, when available, measurements obtained during diagnostic catheterisation. The pressure gradient across the ventricular septal defect was calculated from the maximum flow velocity across it according to a version of the Bernoulli equation; when it was less than 10 mm Hg the ventricular septal defect was defined as non-restrictive. To indicate growth retardation a variable was introduced to represent whether growth was below the third, between the third and 10th, or above the 10th centile. Values were based on patient's weight at clinics during the first 1.5 years of life, using standard growth curves. For patients who

had surgery to close the defect values were based on measurements obtained during the period before the operation. In addition a variable was introduced within the group of patients with non-restrictive ventricular septal defect to measure potential growth delay. This was done by calculating the ratio of the amount of growth observed over a period of time to the amount of growth expected over the same period determined from the 50th weight centile. Finally, the use of diuretics was taken as an indicator of large left to right shunt to categorize the haemodynamic significance of the ventricular septal defect.

Table 5.1 : Comparison of variables to characterise ventricular septal defects inpatients managed conservatively and surgically. Values are numbers (percentages) of patients.

Variable	Conservative (n = 220)	Surgery (n = 43)	Total	P value*
Haemodynamics:				< 0.001
Non-restrictive	12 (5)	43 (100)	55	
Restrictive	208 (95)	0	208	
Morphology:				< 0.001
Muscular	103 (47)	2 (5)	105	
Perimembranous	74 (34)	21 (49)	95	
Perimembranous with extension	20 (9)	16 (37)	36	
Subarterial	0	4 (9)	4	
Unknown	23 (10)	0	23	
Drug treatment:				< 0.001
Yes	25 (11)	33 (77)	58	
No	195 (89)	10 (23)	205	
Growth (centile):				< 0.001
< 10	46 (21)	27 (63)	73	
>= 10	151 (69)	16 (37)	167	
Unknown	23 (10)	0	23	

** All chi-squared tests. Values are based on comparison between conservatively and surgically managed patients for each variable separately.*

5.3.3 Follow-up

Forty three patients were managed surgically (table 5.1). In 41 patients the ventricular septal defect was repaired with a patch, in one patient by direct suture and one patient with multiple ventricular septal defects by banding of the pulmonary

artery. The defect was approached transatrially in all primary repairs. In 28 patients additional minor structural abnormalities were corrected: in 20 patients a patent foramen ovale was closed, in two patients an previously unknown secundum type atrial septal defect was closed, and in six patients a small ductus arteriosus was ligated. The mean age at surgery was 6.4 months (range 1 to 46 months). A trivial residual ventricular septal defect remained in five patients after surgery.

Two hundred and twenty patients were managed conservatively (table 5.1). Spontaneous closure was observed in 65 of them. The mean age at the time the ventricular septal defect was found to have closed was 16.6 months (range 1 to 46 months). At the end of the study the ventricular septal defect was still open in 155 patients, whose mean age was 19.5 months (range 0 to 53 months). No patient died during the follow up.

5.3.4 Statistical analysis

Data are presented as means and ranges unless indicated otherwise. Tests of statistical significance for the comparison of means were performed by the two sample t test. For nominal data chi-squared analysis was used. The Kaplan-Meier method of life table estimation was used to calculate the probability of spontaneous closure within the group of patients who were managed conservatively. The log rank test statistic for equality was used for the comparison of survival distributions based on a single variable. Logistic regression techniques were used to substantiate the influence of the different variables on outcome, in which case the Wald statistic was used for significance testing. In all statistical tests significance was defined as $p < 0.05$.

5.4 Results

Table 5.1 compares data in the patients managed conservatively and surgically. All variables used to characterise the ventricular septal defect differed significantly in the two groups. All ventricular septal defects that were managed surgically were non-restrictive, and the majority of conservatively managed defects were restrictive. When the morphological characteristics were reviewed almost all of the 43 surgically managed defects were of the perimembranous (37 patients), and subar-

terial (four) type. Finally, both growth retardation and the need for supportive medical treatment were more prominent in the surgically managed group.

Table 5.2 : Comparison between ventricular septal defects that closed spontaneously and those that remained open in 220 conservatively treated patients. Values are numbers (percentages) of patients

Variable	Spontaneously closed (n = 65)	Open (n = 155)	Total	P value
Haemodynamics:				NS
Non-restrictive	3 (5)	9 (6)	12	
Restrictive	62 (95)	146 (94)	208	
Morphology:				< 0.001
Muscular	43 (66)	60 (39)	103	
Perimembranous	11 (77)	63 (41)	74	
Perimembranous with extension	2 (3)	18 (12)	20	
Unknown	9 (14)	14 (9)	23	

NS = not significant.

5.4.1 Conservative management

In 208 patients (95%) of the 220 patients managed conservatively the ventricular septal defect was of the restrictive type, the 12 other patients initially had non-restrictive ventricular septal defect (table 5.1). Of all 65 spontaneous closures observed in the study, 62 were restrictive (table 5.2). Three spontaneous closures occurred in the 12 patients with non-restrictive defect. Seven of the nine remaining patients showed a reduction in the size of the defect during follow-up. No such reduction was seen in the two others, the decision to close the ventricular septal defect being made later. The intervention took place after completion of the study.

Only the morphology of the ventricular septal defect differed significantly between patients with spontaneous closures and those with persisting defect. Kaplan-Meier life table analysis estimated the probability of spontaneous closure over time, (figure 5.1). A significant difference ($p < 0.001$) was found between the curves for muscular and perimembranous (both with and without extension) ventricular septal defect. After about 1 year of age, the probability that a muscular ventricular septal defect will be open is 0.72 (SE 0.048; 56 patients remaining). For perimembranous ventricular septal defect this probability is 0.92 (0.031; 61 remaining). In our study

a probability of closure of 0.50 (0.065; 17 remaining) is observed at 2.3 years of age only for muscular ventricular septal defect.

5.4.2 Surgical management

Review of the 43 patients who had surgery showed that 41 patients were operated before the age of 1 year (mean age of 5.2 months (range 2 to 12 months)). The remaining two patients were operated on at the age of 1.3 and 3.9 years, respectively. The reasons for these late interventions were stagnation of the initial reduction in the left ot right shunt during follow-up in one patient and a moderate left ventricular volume overload that was not well tolerated in a defect that had become restrictive before the age of 1 year in the other.

Table 5.1 shows that no patient with restrictive ventricular septal defect was operated on and that all patients managed surgically had non-restrictive defect. However, not all patients with initially non-restrictive ventricular septal defect were operated on. To determine the influence of the variables used to characterise ventricular septal defect on whether to operate or manage conservatively the two groups of patients with non-restrictive ventricular septal defect were compared. The surgically managed group showed significantly more growth delay than the conservatively managed group (0.65 (SD 0.27) vs 0.9 (0.21); $p < 0.001$)

Table 5.3 : Multivariate logistic model for outcome of patients with non-restrictive septal defect

Variable	B (SE)	Odds ratio (significance) *
Drug treatment	-0.236 (0.860)	0.790 (NS)
Morphology:		
Perimembranous (vs muscular)	-0.377 (1.517)	0.686 (NS)
Perimembranous with extension or subarterial (vs muscular)	0.944 (1.619)	2.571 (NS)
Weight (centile):		
< 3rd (vs > 10th)	-0.016 (0.897)	0.984 (NS)
3rd - 10th (vs > 10th)	-0.982 (1.041)	0.375 (NS)
Growth delay (< 60% of expected)	2.599 (1.172)	13.447 (0.01 < p < 0.05)

** For each variable this figure represents the factor by which the odds of operative versus conservative management is multiplied when the variable is present.*

To determine which of the variables might discriminate between the two management groups a multivariate logistic model was calculated. The analysis is shown in table 5.3. The only variable significantly associated with increasing odds of operative management was growth of 60% or less of expected growth. No similar significant influence is found for the other variables.

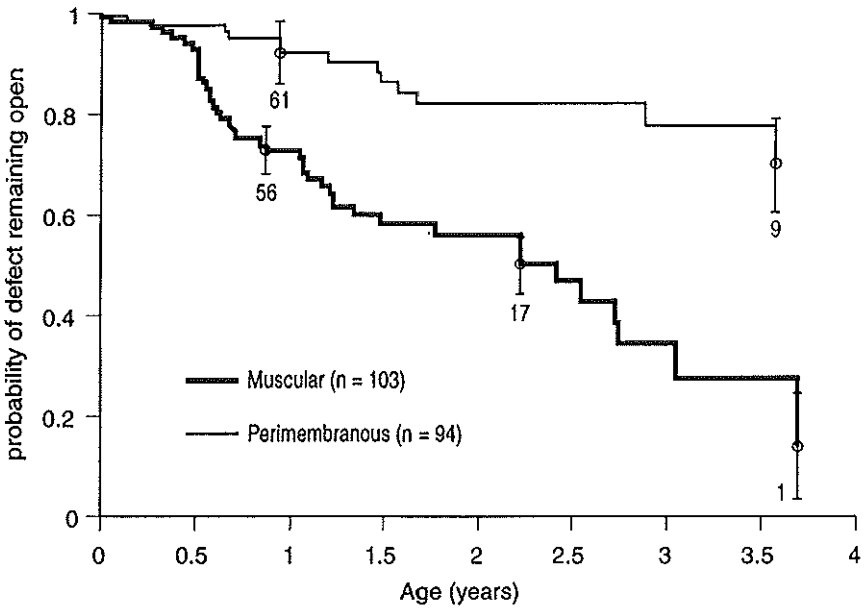

Figure 5.1 : Kaplan-Meier survival curve estimating the probability that a ventricular septal defect will remain open during follow-up in a group of 197 conservatively treated patients with either muscular or perimembranous defect. Vertical bars show the probability with SE and numbers are remaining patients.

5.5 Discussion

5.5.1 Surgical versus conservative management

In our study surgical management within the first year of life is expected in one out of every six patients with isolated ventricular septal defect. All patients managed surgically had non-restrictive ventricular septal defect, but not all patients with such defects were managed surgically: a small number of patients with (initially) non-restrictive ventricular septal defect were managed conservatively. Among

these patients the size of this defect was reduced and in three of the cases the defect closed spontaneously. These two groups were significantly different only with respect to growth rate (table 5.3). Patients with restrictive ventricular septal defect are not operated on within such a short period of time. When a restrictive ventricular septal defect persists over several years of follow up volume overload may be an indication for surgical closure.

5.5.2 Spontaneous closure

Several studies have focused on spontaneous reduction or closure of ventricular septal defects and the influence of size and morphology in this process [5, 7-10]. Results vary considerably among these papers with respect to both incidence and influence of morphology and size. In most series the rate of closure was highest in the first year of life. Only Dickinson et al. found a uniform rate of closure (3% per year over the first 10 years of follow-up) [9]. Moe et al found spontaneous closure in 45% of patients followed up from birth and in 22% of those who had been referred, but size did not influence closure [10]. In another study 75% of the muscular ventricular septal defects closed spontaneously during the first year and 12% showed a significant reduction in diameter [5]. In most studies muscular ventricular septal defects predominate over perimembranous defects, except in the study by Moe et al.

We found that the probability of spontaneous closure is determined by morphology rather than by size of the defect. Actuarial analysis showed that the probability that a ventricular septal defect will close spontaneously during the first year of life is about 3.5 times higher for ventricular septal defects of the muscular type than for defects characterised as perimembranous. Subarterial ventricular septal defects do not spontaneously reduce in size. After the first year of life both types of defects continue to close spontaneously but at a lower rate.

5.5.3 Conclusion

The need for surgical management of isolated ventricular septal defect is mainly determined by the haemodynamic character of the ventricular septal defect. Patients born with non-restrictive defects have a high probability of needing surgery. Because early primary closure is now possible with both low mortality (in our se-

ries no patient died) and low morbidity [11, 12] delaying surgery is no longer indicated when patients present with overt growth delay or cardiac failure. Favourable improvement in postoperative growth after early surgical intervention as described by Weintraub et al supports this policy of early intervention [13]. However, because spontaneous reduction in size or even closure is not influenced by the size of the defect conservative management may be indicated even for large ventricular septal defects, especially if the defect is in the muscular septum, provided the clinical status of the patient permits a protracted treatment regimen.

We found that the morphology of the ventricular septal defect determines the probability of spontaneous reduction in size and provides an estimate of the period over which this reduction can be expected. Finally, we found that a sophisticated pediatric database management system facilitates clinical research over relatively short periods of follow-up, leading to relevant data for decision making.

5.6 References

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Management of valvular aortic stenosis
A comparison between valvulotomy and balloon dilatation

6

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6.1 Abstract

Controversy exists with respect to the preferred method of initial treatment of isolated aortic valve stenosis. The impact of introduction of the balloon dilatation technique on the management regimen of aortic valve stenosis and its subsequent effect on the clinical status of patients was assessed.

Two groups of patients with non-critical, isolated aortic valve stenosis were compared and were studied over a similar period of time before (n = 45, pre-balloon era) and after (n = 50, balloon era) the introduction of balloon dilatation in our center. Patients from the pre-balloon era had a higher probability of earlier management resulting in a larger fraction of patients with transvalvular gradients < 50 mmHg at the end of follow-up (82%, compared to 59%; p = 0.02). In the pre-balloon era patients were managed at a higher mean transvalvular gradient prior to valvulotomy (89 SD 22 mmHg, compared to 67 SD 25; p = 0.03). Patients from the pre-balloon era managed by balloon dilatation after introduction of this technique (n = 7) were added to 19 patients managed during the balloon era with follow-up data. These 26 patients were compared with the patients managed by surgery. Pre-management repolarization disturbances were more prominent in patients managed by surgery (50%, vs 15%; p = 0.03). With respect to both freedom from reintervention and incidence of aortic regurgitation after management both groups were comparable.

Surgical valvulotomy and balloon dilatation are comparable treatment regimens for the management of isolated non-critical aortic valve stenosis. However, patients managed by balloon dilatation are managed earlier at lower gradients, keeping the patient population at a lower (residual) gradient. Balloon dilatation provides an effective alternative to valvulotomy that can delay future surgical interventions.

6.2 Introduction

The introduction of balloon dilatation as an alternative for surgical management of aortic valve stenosis in neonates, infants, and children has given rise to questions with respect to the preferred method of treatment [1, 2]. If efficacy, morbidity, and mortality of balloon dilatation are comparable with the results of surgical treatment, aortic balloon dilatation might be the preferred form of initial management. However, risks associated with this technique, such as the occurrence of valvular regurgitation, persistence of a substantial gradient, or femoral artery thrombotic complications, may induce additional morbidity, or even necessitate surgical management. Controversy arises when these complications are balanced against a potential advantage of balloon dilatation in terms of repeatability of the procedure and achieving and maintaining acceptable transvalvular pressure gradients without the need for surgery at a young age.

For an accurate assessment of the differences between both treatment regimens, randomized comparison of both treatment regimens and long-term follow-up is necessary. However, several considerations render such studies impossible. Although the results of balloon dilatation in both infants and children are reported frequently [1, 3-12] a direct comparison with the results of surgical management have been rarely made [2, 13], and follow-up is usually limited.

In this study we compared patients with non-critical isolated aortic valve stenosis managed over a similar period of time before and after the introduction of balloon dilatation in our center. Firstly, the impact of introduction of balloon dilatation on the management strategy of non-critical isolated valvular aortic stenosis in our center and its subsequent effect on the clinical status of the patient population was

studied. Secondly, a comparison between balloon dilatation and surgical management was made with respect to the efficacy of both treatment regimens.

6.3 Methods

6.3.1 Patient data

We studied a consecutive series of 95 patients who were born and presented with isolated, non-critical aortic valve stenosis between January 1979 and January 1995 at the Division of Pediatric Cardiology of the Sophia Children's Hospital in Rotterdam. From May 1987 onwards balloon dilatation of the aortic valve was adopted as the initial treatment for valvular aortic stenosis in our center. Based on this date the study period was divided into 2 consecutive periods. Between January 1979 and May 1987, the pre-balloon era, the initial treatment regimen consisted of surgical, open valvulotomy. Forty five of the 95 patients in our study group were born and presented during this period and represent the pre-balloon era group. Within this group surgical valvulotomy was performed in 10 patients. The remaining 50 of the 95 patients in our study were born and presented during the following period between May 1987 and January 1995, representing the balloon era group. Balloon dilatation was indicated in 20 patients in this group. After adoptation of the balloon valvuloplasty technique in May 87 during the follow-up period for the patients from the balloon era, 7 additional balloon procedures were performed in patients from the pre-balloon era study period that had been treated conservatively during the pre-balloon era.

End of follow-up was determined by the last visit before the end of the study period, regardless of any reinterventions or operations that followed initial management. End of follow-up was also reached when a patient died before the end of the study period. Patients with critical aortic stenosis and additional structural heart abnormalities were excluded from the study. Critical aortic valve stenosis was judged to be present when a duct dependent systemic circulation existed. Baseline characteristics of both groups are summarized in table 6.1.

6.3.2 Comparisons made

Between the two study groups and management regimens three comparisons were made: Firstly, patients, both managed and not managed, from the pre-balloon and balloon era were compared with respect to their baseline and follow-up characteristics with special emphasis to the clinical status at the end of follow-up. Secondly, a comparison was made between patients from the pre-balloon era managed by surgical valvulotomy and patients from the balloon era managed by balloon dilatation. Finally, this comparison was repeated while including the 7 additional patients from the pre-balloon era who were managed by balloon dilatation during the balloon era study period. These 7 patients had been managed conservatively previously.

6.3.3 Data selection & diagnostic methods

The selection of the study patients was facilitated by a dedicated database management system that utilizes an extensive knowledge base of congenital heart disease terminology [13, 14]. For each patient additional data were obtained from clinical, echocardiographic, and catheterization records.

Repolarization was judged to be abnormal if horizontal ST segment changes in the electrocardiogram were equal to or more than 2 mm. For patients managed by surgery and balloon dilatation the transvalvular pressure gradients prior to valvulotomy or balloon dilatation were available. In all cases this gradient had been determined as the peak systolic pressure gradient obtained during cardiac catheterization. The transvalvular pressure gradients obtained during follow-up were all based on continuous-wave Doppler measurements, calculated from peak flow velocities (using the modified Bernoulli equation).

At the end of follow-up the hemodynamic status of the patients were described by the transvalvular gradient and the presence or absence of aortic regurgitation. Pressure gradients were based on Doppler measurements from the most recent outpatient visit before the end of follow-up. This measurement was used to calculate the gradient reduction between the pressure difference prior to surgery and the residual gradient present at the end of follow-up. Regurgitation was evaluated semi

quantitatively on a scale of 0 (no regurgitation) to 3 (severe regurgitation) based on Doppler echocardiographic tracings [12].

6.3.4 Data analysis

Data are presented as mean values with standard deviation and range. Univariate tests of statistical significance for the comparison of continuous variables were performed by the two sample t-test or the Mann-Whitney non-parametric test when samples were found to be not-normally distributed. For categorical data chi-squared analysis or the Fisher exact test were employed where appropriate. Actuarial analyses of freedom from management and freedom from reintervention were performed by means of the Kaplan-Meier method of life table estimation. The log-rank statistic was used to compare different survival curves based on a single variable. In all tests, statistical significance was defined at $p < 0.05$.

6.4 Results

6.4.1 Comparison between all patients from the pre-balloon era and all patients from the balloon era (table 6.1, figure 6.1 & 6.2)

6.4.1.1 Patients from the pre-balloon era

Forty five patients were born and presented between January 1979 and May 1987, the pre-balloon era study period. During this period surgical valvulotomy was performed in 10 patients (22%). At the end of the study period there had been no intervention in 35 patients. No re-operations were performed during the study period and no deaths were recorded. In this study group, 8 additional procedures were performed during the balloon era study period. These procedures consisted of 7 balloon dilatations and 1 Ross operation (pulmonary autograft in the aortic position with a homograft in the pulmonary position). In this latter patient no balloon dilatation was performed because of a grade 3+ aortic valve regurgitation. Re-operations were performed in 4 patients who had been operated upon during the pre-balloon era. At the end of the balloon era, the number of patients managed either by surgery or balloon dilatation had increased from 10 (22%) at the end of the pre-balloon era follow-up period to 18 (40%).

Table 6.1 : Comparison of variables between all patients (percentages) from the pre-balloon era and the balloon era.

Variable	Pre-balloon era (n = 45)	Balloon era (n = 50)	P value
Age at surgery / balloon dilatation	1.5y SD 1.9y range 10d - 7.3y	1.1y SD 1.4y range 1d - 6.3y	NS
Managed	10 (22)	20 (40)	NS
Duration of follow-up	2.9y SD 2.0y range 1m - 8.3y	3.0y SD 1.7y range 1.7m - 6.4y, n = 49 *	NS
Gradient end of FU (mmHg)	45 SD 20 range 10 - 80, n = 39 *	39 SD 15 range 15 - 65, n = 49 *	NS
Gradient category end of FU (mmHg):			< 0.05
<= 50	23 (59)	40 (82)	
> 50	16 (41)	9 (18)	
Mortality	0	2 (4)	NS

** No follow-up in a patient who died shortly after the balloon procedure. SD = standard deviation; NS = not significant; FU = follow-up; d = days; m = months; y = years.*

6.4.1.2 Patients from the balloon era

Fifty patients were born and presented between May 1987, the introduction of the balloon dilatation technique, and January 1995. Balloon dilatation was indicated in 20 patients (40%). The balloon dilatation procedure was accomplished in 19 of them (95%). In one patient the balloon catheter could not be positioned across the valve and surgical valvulotomy was performed 7 days later. Within the balloon era group there were 2 patient deaths. One patient died four days after balloon dilatation as the result of a massive hemorrhage from the catheter entry site. A second patient died 3.4 months after the initial balloon procedure as a result of poor left ventricular function. There were 4 reinterventions in this group consisting of surgical valvulotomy in 3 and repeated balloon dilatation in one patient respectively.

In table 6.1 a comparison is made between patients from the pre-balloon era and patients from the balloon era. With respect to age at presentation, number of patients managed, duration of follow-up, mortality, and gradient at the end of follow-up no statistically significant differences were found. Although the proportion of

patients managed during the pre-balloon era was almost half the proportion of patients managed during the balloon era, this apparent higher management frequency during the balloon era was not significant. Freedom from management over follow-up in both groups was assessed by Kaplan-Meier analysis as shown in figure 6.1. A statistically significant difference between both curves was found, indicating a higher probability of early management in patients from the balloon era compared with patients from the pre-balloon era. However, when follow-up for the pre-balloon era group was extended with follow-up data over the balloon era period as shown in figure 6.2 this difference in probability of management between both groups disappeared. Although a comparison of the mean transvalvular gradient in both groups at the end of follow-up revealed no statistical differences, a significantly larger proportion of patients managed by balloon dilatation had gradients equal to or less than 50 mmHg.

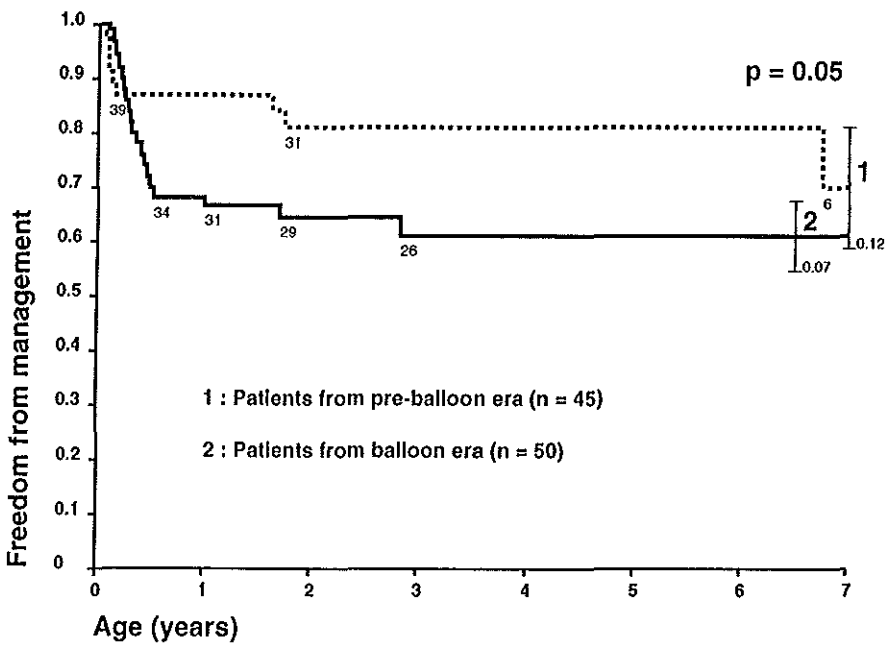

Figure 6.1 : Kaplan-Meier curves of freedom from management for patients with aortic valve stenosis. Group 1 represents patients who presented and were followed during the pre-balloon era (n = 45) and group 2 represents patients who presented and were followed during the balloon era (n = 50). Numbers underneath the lines indicate the number of patients remaining in the study at that moment. Numbers at the vertical lines indicate the estimated standard error around the probability values at 7 years.

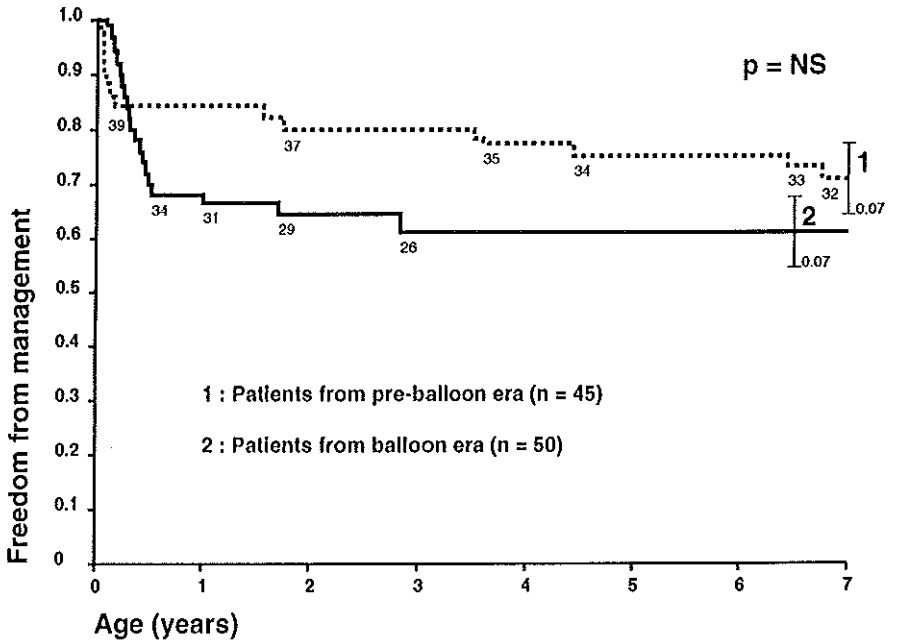

Figure 6.2 : Kaplan-Meier curves of freedom from management for patients with aortic valve stenosis. Group 1 represents patients who present during the balloon (n = 45) era. Group 2 represents patients who presented and were followed during the balloon era (n = 50). Numbers underneath the lines indicate the number of patients remaining in the study at that moment. Numbers at the vertical lines indicate the estimated standard error around the probability values at age 7 years. NS = not significant.

6.4.2 Comparison between patients from the pre-balloon era managed by surgical valvulotomy and patients from the balloon era managed by balloon dilatation (table 6.2)

In table 6.2 a comparison is made between patients managed during the pre-balloon era by means of surgical valvulotomy and patients managed during the balloon era by means of balloon dilatation. Only with respect to the transvalvular gradient, measured by cardiac catheterization prior to either surgical valvulotomy or balloon dilatation, a significant difference between both study groups was found, with a higher mean gradient in patients managed by surgical valvulotomy.

Table 6.2 : Comparison of variables between patients (percentages) managed by surgical valvulotomy during the pre-balloon era and managed by balloon dilatation during the balloon era.

Variable	Pre-balloon era (n = 10)	Balloon era (n = 20)	P value
Age at surgery / balloon dilatation	1.8y SD 2.9y range 23d - 7.8y	0.9y SD 1.8y range 27d - 8.1y	NS
Pre-management gradient (mmHg)	89 SD 22 range 70 - 140	67 SD 25 range 35 - 120	< 0.05
Pre-management repolarization disturbances	5 (50)	4 (20)	NS
Duration of FU	3.2y SD 2.7y range 2.8m - 7.8y	3.1y SD 2.0y range 3.4m - 6.4y, n = 19 **	NS
Gradient at end of FU (mmHg)	52 SD 17 range 30 - 80	41 SD 14 range 20 - 65, n = 19 **	NS
Gradient reduction over FU (mmHg)	38 SD 15	27 SD 24, n = 18 * **	NS
Gradient reduction at end of FU (mmHg):			NS
<= 50	5 (50)	15 (79)	
> 50	5 (50)	4 (21)	
Aortic regurgitation at end of FU:			NS
None or mild	8 (80)	10 (53)	
Moderate	2 (20)	7 (37)	
Severe	0	2 (10)	
Mortality	0	2 (10)	NS

** Missing pre-balloon gradient in a patient where no valve passage was achieved. ** No follow-up in a patient who died shortly after the balloon procedure. SD = standard deviation; NS = not significant; FU = follow-up; d = days; m = months; y = years.*

6.4.3 Comparison between patients managed by surgical valvulotomy and patients managed by balloon dilatation (table 6.3, figure 6.3)

In table 6.3 a comparison is made between the 10 patients managed by surgical valvulotomy and 26 patients managed by balloon dilatation (19 patients from the balloon era with follow-up data together with the 7 patients from the pre-balloon

era who were managed by balloon dilatation after May 1987). Only with respect to the presence of repolarization disturbances prior to management a statistical difference was found with more repolarization disturbances in patients managed by surgical valvulotomy. With respect to the probability of reintervention after initial management a comparison between both groups was made by means of Kaplan-Meier analysis as shown in figure 6.3. Follow-up for the patients managed by surgery consisted of data from both the pre-balloon and the balloon era. Between both curves no statistical difference was found.

Table 6.3 Comparison of variables between patients (percentages) managed by surgical valvulotomy and balloon dilatation. Analysis is restricted to patients with follow-up data.

Variable	Surgical valvulotmy (n = 10)	Balloon dilatation (n = 26)	P value
Pre-management gradient (mmHg)	89 SD 22 range 70 - 140	74 SD 25 range 35 - 120, n = 25 *	NS
Pre-management repolarization disturbances	5 (50)	4 (15)	< 0.05
Gradient at end of FU (mmHg)	52 SD 17 range 30 - 80	40 SD 14 range 15 - 65	NS
Gradient reduction over FU (mmHg)	38 SD 15	33 SD 27, n = 25 *	NS
Reinterventions	0	5 (19)	NS
Gradient category at end of FU (mmHg):			NS
<= 50	5 (50)	21 (81)	
> 50	5 (50)	5 (19)	
Aortic regurgitation at end of FU:			NS
None or mild	8 (80)	14 (54)	
Moderate	2 (20)	10 (38)	
Severe	0	2 (8)	
Mortality	0	2 (8)	NS

** Missing pre-balloon gradient in a patient where no valve passage was achieved. SD = standard deviation; NS = not significant; FU = follow-up; d = days; m = months; y = years.*

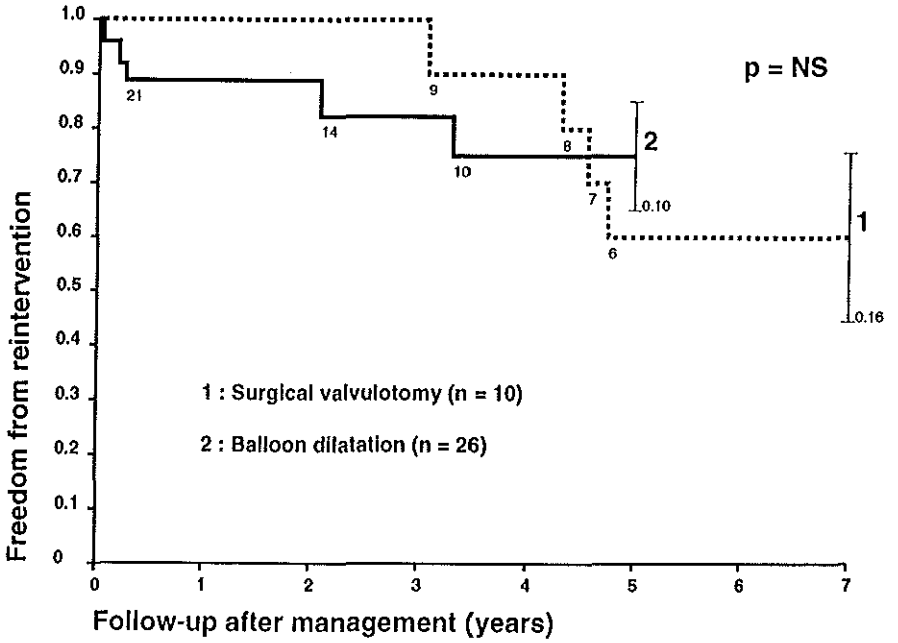

Figure 6.3 : Kaplan-Meier curves of freedom from re-intervention for patients with aortic valve stenosis. Group 1 represents patients managed by surgical valvulotomy (n = 10) and group 2 represents patients managed by balloon dilatation (n = 26). Follow-up for group 1 included the pre-balloon era as well as the balloon era. Numbers underneath the lines indicate the number of patients remaining in the study at that moment. Numbers at the vertical lines indicate the estimated standard error around the probability values at age 5 years for group 2 and age 7 years for group 1. NS = not significant.

6.4.4 Femoral artery complications

In 5 out of 26 patients (19%) managed by balloon dilatation, femoral artery thrombosis occurred. Four of these were successfully treated with thrombolytic therapy. In one patient streptokinase did not have any effect and therapy was discontinued. However, fatal bleeding occurred more than 12 hours after discontinuation. No peripheral artery complications were observed in patients older than 5 months.

6.5 Discussion

The final outlook for patients with congenital aortic valve stenosis is associated with a high incidence of reoperation and valve replacement [16-19]. Because of the

limitations of valve replacement at a young age [20] a palliative approach for management of valvular aortic stenosis in the pediatric age group is needed. Recurrent palliative procedures, such as surgical valvulotomy or balloon dilatation, surely delay the timing of valve replacement but do not replace it. Long standing significant left ventricular pressure overload may lead to irreversible damage to the myocardium thus inducing impaired left ventricular function. Definite criteria on the reversibility of myocardial dysfunction, specifically in children with moderate pressure gradients, are lacking. However, the aim to prevent a persisting significant pressure gradient across the aortic valve by early management is attractive. Therefore, the challenge in this group of patients is to reduce the left ventricular pressure overload early, without the side-effects of a surgical procedure such as adhesions, that may complicate a future operation. Aortic balloon valvuloplasty has been introduced as an alternative for surgical palliation [1, 3, 21]. These aspects explain the change in policy for children with aortic valve stenosis since the introduction of balloon dilatation.

Our data indicate that with the introduction of balloon dilatation for the management of isolated non-critical aortic valve stenosis in our center, patients managed during the balloon era had a higher probability of management at a lower transvalvular gradient than patients managed during the pre-balloon era. This change in policy has resulted in a higher proportion of patients with gradients less than or equal to 50 mmHg managed in the balloon era than that of patients managed during the pre-balloon era. This 50 mmHg level is recognized as an acceptable maximum gradient for conservative follow-up [19, 22].

With respect to the efficacy of both modes of therapy, comparable results are achieved by means of both techniques in terms of gradient reduction, aortic regurgitation after management, incidence and probability of reintervention, and mortality. However, it appears that pre-treatment ST segment changes in the electrocardiogram indicative of myocardial strain are less prominent in patients managed by balloon dilatation. This probably reflects management at an earlier stage in the process of impending myocardial dysfunction [23].

The size of reduction of the transvalvular gradient after balloon dilatation in our series is comparable to the findings of others [7, 10, 11, 24]. The observed tendency to

more aortic regurgitation after balloon dilatation compared with aortic regurgitation after surgical valvulotomy did not reach statistically significant levels, although such a relationship has been found by many others [1, 4, 5, 10, 12, 19, 22, 25]. Nevertheless, induction of severe aortic regurgitation by balloon dilatation in 3 of our patients is an important sequellum that required surgical reintervention, a Ross procedure, in one patient. Therefore, induction of serious regurgitation constitutes an important complication and this risk must be balanced against a presumed benificial effect on the myocardium by preventing prolonged pressure overload caused by larger transvalvular gradients.

6.5.1 Other studies

Studies that compare surgical and balloon valvuloplastic management of patients with valvular aortic stenosis are rare [13, 2]. Studies by Zeevi et al. and Mosca et al. do compare surgical and balloon management techniques, but their studies deal with patients that had critical aortic stenosis. As in our series, in these studies comparable results for both management regimens were found.

6.5.2 Study limitations

The most important limitations to our study are twofold. We compared patients from non-randomized groups and different time periods. Also the number of patients is small. Secondly, comparison of peak instantaneous Doppler gradients with peak to peak gradients measured at cardiac catheterization may seem misleading. Nevertheless we have used this difference as a measure of pressure reduction for the comparison of efficacy of balloon dilatation versus surgical management. For both groups these differences were based on pressure gradients measured invasively before management, and Doppler derived gradients after management, at the end of follow-up. Such a comparison seems legitimate because the error in gradient reduction that arises from the use of data derived from 2 different measurement techniques has been made to the same extent in both groups.

6.5.3 Conclusions

Based on our findings we conclude that both balloon dilatation and surgical valvulotomy are comparable treatment regimens for the management of isolated non-critical aortic valve stenosis. However, the introduction of balloon dilatation had

two important effects. Firstly, patients managed by balloon dilatation proved to have a higher probability of management at lower transvalvular gradients compared with patients managed during the pre-balloon era. Secondly, as a result a larger fraction of patients had gradients equal to or less than 50 mmHg. Both aspects are presumed to have a benificial effect on the preservation of myocardial function.

We therefore argue that balloon dilatation for valvular aortic stenosis at an earlier stage, maintaining the residual gradient at a lower level provides an effective alternative that preserves myocardial function, and can delay future surgical interventions.

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Arterial hypertension after surgical management of coarctation in infancy

7

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7.1 Abstract

This study aimed to determine risk factors for both recurrent coarctation and systolic hypertension at the end of follow-up after coarctation repair in the first year of life, and to assess incidence and risk factors for systolic hypertension in the absence of recurrent coarctation. The relationship between late hypertension and recurrent coarctation and the influence of aortic arch morphology on the development of these sequelae remains controversial.

We studied a consecutive series of 68 patients managed for aortic coarctation in their first year of life over a period of 8 years. After surgery, follow-up data were available for all patients over a mean period of 3.1 SD 1.9 years. During follow-up in 10 patients (15%, CI 6 - 22%) recurrent coarctation was found. Regression analysis identified weight at surgery and preoperative transverse arch hypoplasia as relative risk factors for recoarctation. In 16 patients (24%, CI 13 - 34%) systolic hypertension was present at the end of follow-up. Only recurrent coarctation was related significantly with hypertension. Even in a subgroup consisting of patients corrected for circumscript lesions and without a history of recurrent coarctation, 24% (CI 7 - 29%) were hypertensive at the end of follow-up. No risk factors for their hypertension were identified.

Results indicate that the presence of systolic hypertension at the end of follow-up is related to recurrent coarctation but not to aortic arch morphology. Furthermore, systolic hypertension is present in a substantial fraction of patients managed for circumscript lesions without a history of recurrent coarctation. It is argued that determinants other than recurrent coarctation and aortic arch morphology play an important role in the pathogenesis of systolic hypertension and that their influence becomes already apparent after short periods of follow-up in patients operated upon at young age.

7.2 Introduction

Despite improved management and successful initial surgical repair of aortic coarctation in children, recurrent coarctation, late systolic hypertension, and related long-term cardiovascular morbidity after initial successful surgical repair remain important aspects of the clinical history [1-4]. Nevertheless, studies that investigate risk factors for recurrent coarctation and late hypertension in children with coarctation managed in their first year of life are rare. In many surveys age at management is well beyond or only partially during infancy [4-6] or infants were managed by more than one surgical technique [7]. In several studies young age at surgery has been identified as a prominent risk factor for the prevalence of recurrent coarctation [3, 8-10]. With respect to the development of late hypertension after repair a more advanced age at the moment of surgical correction is recognised as risk factor [3, 9, 11]. With respect to the morphology of the aortic arch, associations between underdevelopment of parts of the aortic arch and aortic coarctation have been found, especially in symptomatic neonates when coarctation is associated with additional cardiac anomalies, but also in isolated coarctation [12-16]. Arch hypoplasia has been related to increased mortality and recoarctation by some authors [17-19] but again questioned by others [12, 20, 21]. Still the relationship between late hypertension and recurrent coarctation supported by some authors [8, 10, 22, 23] but questioned by others [24-26] and the influence of aortic arch morphology on the development of both sequelae remains unclear.

We therefore initiated this survey that exclusively deals with a consecutive series of patients with aortic coarctation managed before the age of 1 year by means of a

single surgical technique (resection and extended end-to-end anastomosis). In addition to determination of risk factors for both recurrent coarctation and the presence of systolic hypertension at the end of follow-up, emphasis will be put on the incidence and potential risk factors of systolic hypertension at rest in the absence of recurrent coarctation.

7.3 Patients and methods

7.3.1 Patients

We studied a consecutive series of 68 patients born between January 1, 1986 and January 1, 1994 who underwent surgical repair of aortic coarctation by means of resection and extended end-to-end anastomosis in the first year of life. The study population consisted of 41 (60%) male and 27 female patients. Mean age at presentation was 1.0 months (SD 1.4 months, range 1 day to 6.4 months). Surgery for aortic coarctation was performed at a mean age of 2.2 months (SD 2.5 months, range 6 days - 9.4 months). Thirty-eight of the 68 procedures (56%) were on neonates less than 1 month of life, 14 (21%) were on infants between 1 and 3 months, and the remaining 16 procedures (23%) were on patients older than 3 months of life. In 36 patients (52%) prostaglandin E1 administration prior to surgery was necessary to sustain adequate systemic circulation prior to surgery. These patients were operated upon at a mean age of 20.1 days (SD 12.2 days, range 6 days - 2.0 months).

In 45 patients (69%) isolated aortic coarctation, with or without a patent arterial duct, was present. In these patients the procedure was performed through a left posterolateral thoracotomy. In 21 patients (31%) additional congenital intracardiac anomalies were present. In all these patients a ventricular septal defect was present in addition to the aortic coarctation. Nine patients also had an atrial septal defect and in 1 patient mild valvular aortic stenosis was present that did not require intervention during the study period. In 8 of the 21 patients with additional structural anomalies correction of the aortic coarctation was performed via posterolateral thoracotomy. In 7 of these patients correction of the intracardiac anomalies was performed during a second surgical procedure 3 weeks to 2.1 years after the initial coarctation repair. In the remaining 13 of the 21 patients both the aortic coarctation

and the intracardiac defects were corrected in a single stage procedure through a median sternotomy. Patients with other, complex cardiac anomalies were excluded from the study.

The dataset for analysis was obtained from our departmental pediatric cardiology database management system. Analysis of the database was performed by SmaCS, an information system developed for the management of both complex congenital heart terminology and retrieval of patient data [27].

7.3.2 Follow-up

Of all patients follow-up data were available. End of follow-up was defined as the most recent follow-up visit before the end of the study, or the date of death. Mean age at the end of the study was 3.2 years (SD 1.9 years, range 4.5 months - 7.8 years). Mean duration of follow-up after coarctation repair was 3.1 years (SD 1.9 years, range 4.0 months - 7.7 years). No patients were on antihypertensive medication.

7.3.3 Aortic coarctation morphology

Fifty-two patients (76%) underwent cardiac catheterization prior to surgery. Preoperative morphology of the aortic arch was assessed from cineangiogram and based on measurements obtained from the lateral view. The diameter of the descending aorta, measured approximately 3 ribs below the coarctation site was used as a reference. This measurement location was chosen to avoid measuring possible post stenotic dilatation. The diameters of the distal transverse aortic arch (between the left carotid artery and left subclavian artery) and the aortic isthmus were measured and expressed as ratios of the descending aorta diameter. Measurements of the aortic isthmus consisted of either the largest diameter of the segment between the left subclavian artery and the coarctation in case of a circumscript stenosis or the overall diameter of the segment in case the aortic coarctation was formed by a hypoplastic segment. When the ratio was less than 50% of the descending aorta, the respective arch segment was regarded as hypoplastic. In 8 patients a hypoplastic distal transverse aortic arch and in 5 patients a hypoplastic aortic isthmus was found. None had both.

In addition to these ratios, the coarctations were characterized as circumscript or consisting of a hypoplastic segment with or without a circumscript narrowing. This information was obtained from surgical reports and was available for all patients, including the 17 patients in whom no preoperative catheterization was performed.

7.3.4 Definitions

Hypertension: systolic blood pressure at the end of follow-up, measured in the right arm at rest during routine follow-up examination using an appropriately sized cuff, equal to or exceeding the 95th percentile based on age and sex related normal values for systolic blood pressure.

Recurrent coarctation: defined as either residual coarctation present directly after surgery or recoarctation. True recoarctation was considered to be present when a blood pressure difference of at least 20 mmHg was found between right arm and legs that was undetected directly after surgery and not present at the first postoperative evaluation. In addition to an arm - leg pressure difference, recoarctation was confirmed by echocardiography, based a Doppler peak systolic velocity measurement across the coarctation repair site of more than 2 m/s.

7.3.5 Statistical analysis

All data are summarized as mean with standard deviation and range. Proportions of patients with recurrent coarctation and systolic hypertension at the end of follow-up are reported with 95% confidence intervals (CI). Comparison of continuous variables between groups were made by the Student t-test or the Mann-Whitney U test where appropriate. Categorical data were compared using chi-squared analysis or Fisher's exact testing where appropriate. Multivariate relative risk analysis was performed with logistic regression for residual coarctation and Cox regression for recoarctation. Variables were used in regression analysis when their probability values in univariate comparison were significant. In all statistical tests a probability value of less than 0.05 was considered to be significant.

7.4 Results

7.4.1 Mortality

In our series there were no surgical deaths. One female patient with persistent pulmonary hypertension died 4 months after successful coarctation repair.

Table 7.1 : Comparison of variables between patients (percentages) with and without a history of recurrent coarctation among patients managed for aortic coarctation in the first year of life (n = 68).

Variable	Recurrent CoAo (n = 10)	No recurrent CoAo (n = 58)	P value
Duration of FU	73.4m SD 22.6m	32.9m SD 25.3m	NS
Birth weight (kg)	3.1 SD 0.9	3.2 SD 0.6, n = 52 *	NS
Age at surgery	16.2d SD 3.7d	74.2d SD 80.6d	< 0.05
Weight at surgery (kg)	3.1 SD 0.8	4.5 SD 0.8, n = 52 **	< 0.05
Patient sex:			
Male	6 (60)	35 (60)	NS
Female	4 (40)	23 (40)	
Preoperative prosta-glandin	9 (90)	35 (60)	< 0.05
Isolated CoAo	5 (50)	40 (69)	NS
CoAo with intracardiac defects	5 (50)	18 (31)	
Lateral thoracotomy	7 (70)	48 (83)	NS
Median sternotomy	3 (30)	10 (17)	
Ration AoIst / DAo (%)	58 SD 18, n = 8 ***	68 SD 13, n = 44 ***	NS
<= 50%	4 (50)	4 (9)	< 0.05
Ration TrA / DAo (%)	57 SD 10, n = 8 ***	70 SD 12, n = 44 ***	< 0.01
<= 50%	3 (38)	2 (5)	< 0.05
Circumscript CoAo	6 (60)	52 (90)	< 0.05

** Weight at birth unknown in 6 patients. ** Weight at surgery unknown in 6 patients. *** Only patients with preoperative cardiac catheterization. SD = standard deviation; NS = not significant; FU = follow-up; AoIst = aortic isthmus; DAo = descending aorta; TrA = Distal transverse aortic arch; CoAo = Aortic coarctation; d = days; m = months.*

7.4.2 Recurrent coarctation (table 7.1)

In 10 patients (15%, CI 6 - 22%) recurrent coarctation was present during follow-up. In 4 of these patients there had been evidence of residual coarctation directly following the surgical procedure. In the remaining 6 patients a true recoarctation developed during follow-up after a mean follow-up period of 4.4 months (SD 2.2, range 35 days - 8.0 months).

The 4 patients with residual coarctation were all managed by balloon angioplasty. In one patient a 2nd surgical coarctectomy was performed when after 3 balloon angioplastic procedures over a period of 3.2 years inadequate relief of pressure gradient across the residual coarctation was accomplished.

Three of the 6 patients with recoarctation were managed by balloon angioplasty. In one of these 3 patients the procedure proved inadequate and a second surgical correction was performed 4 months later at age 8.5 months. In another of these 3 patients recoarctation reappeared 5 years after the initial successful balloon procedure. This patient was again managed by balloon angioplasty successfully. The remaining 3 patients with recoarctation were not managed during the study period. In two of them balloon angioplasty was performed after seclusion of the study.

In table 7.1 a comparison is made between patients with and without a history of recurrent coarctation based on a number of clinical characteristics. Significant differences between both groups were found with respect to age and weight at surgery, preoperative necessity for prostaglandin, coarctation type, mean diameters of the distal transverse aortic arch and aortic isthmus, and number of patients with hypoplastic transverse aortic arch and aortic isthmus. Separate regression analyses were performed to identify risk factors for recoarctation and residual coarctation. These analyses identified weight at surgery (coefficient -6.3 SE 3.2, $p = 0.05$) and preoperative hypoplasia of the transverse arch (coefficient -8.3 SE 4.1, $p = 0.05$) as significant relative risk factors for the development of recoarctation, but failed to identify risk factors for residual coarctation.

Table 7.2 : Comparison of variables between patients (percentages) with and without systolic hypertension at the end of follow-up among patients managed for aortic coarctation in the first year of life (n = 68).

Variable	Hypertension (n = 16)	No hypertension (n = 52)	P value
Duration of FU	34.9m SD 19.3m	37.3m SD 24.1m	NS
Birth weight (kg)	3.1 SD 0.8, n = 15 *	3.2 SD 0.7, n = 47 *	NS
Age at surgery	54.3d SD 71.1d	69.1d SD 79.3d	NS
Weight at surgery (kg)	4.1 SD 2.0, n = 15 **	4.3 SD 1.8, n = 51 **	NS
Sex:			NS
Male	11 (69)	30 (58)	
Female	5 (31)	22 (42)	
Isolated coarctation	9 (56)	36 (69)	NS
Coarctation with intracardiac defects	7 (44)	16 (31)	
Posterolateral thoracotomy	13 (81)	42 (81)	NS
Median sternotomy	3 (19)	10 (19)	
History of recurrent CoAo	5 (31)	5 (10)	< 0.05
Ration AoIst / DAo (%)	62 SD 18, n = 13 ***	68 SD 13, n = 39 ***	NS
<= 50%	4 (31)	4 (10)	NS
Ration TrA / DAo (%)	68 SD 11, n = 13 ***	68 SD 14, n = 39 ***	NS
<= 50%	1 (8)	4 (5)	NS
Circumscript CoAo	12 (75)	46 (88)	NS

** Weight at birth unknown in 6 patients. ** Weight at surgery unknown in 2 patients. *** Only patients with preoperative cardiac catheterization. SD = standard deviation; NS = not significant; FU = follow-up; AoIst = aortic isthmus; DAo = descending aorta; TrA = Distal transverse aortic arch; CoAo = Aortic coarctation; d = days; m = months.*

7.4.3 Systolic hypertension (table 7.2 and 7.3)

At the end of follow-up in 16 patients (24%, CI 13 - 34%) systolic hypertension was present. In table 2 a comparison is made between patients with and without systolic hypertension at the end of follow-up based on a number of characteristics. Only with respect to a history of recurrent coarctation a significant difference was

found between both groups, hypertension being more frequent in patients with a history of recurrent coarctation. Within the population of 68 study patients a group of 50 patients was identified that had circumscript lesions and no history of recurrent coarctation. Within this group 9 patients (18%, CI 7 - 29%) were hypertensive at the end of follow-up without signs of recurrent coarctation. In Table 3 a comparison is made among these 50 patients divided into those with and without hypertension at the end of follow-up. No significant differences were found between both groups.

Table 7.3 : Comparison of variables between patients (percentages) with and without systolic hypertension at the end of follow-up among patients managed for circumscript aortic coarctation (n = 50).

Variable	Hypertension (n = 9)	No hypertension (n = 41)	P value
Duration of FU	40.2m SD 20.9m	37.2m SD 23.7m	NS
Birth weight (kg)	2.1 SD 0.8, n = 8 *	3.2 SD 0.6, n = 37 *	NS
Age at surgery	88.3d SD 86.5d	79.3d SD 83.5d	NS
Weight at surgery (kg)	5.1 SD 2.3, n = 8 **	4.5 SD 1.9	NS
Preoperative prostaglandin	2 (22)	15 (37)	NS
Isolated CoAo	7 (78)	32 (78)	NS
CoAo with intracardiac defects	2 (22)	9 (22)	
Ration AoIst / DAo (%)	69 SD 11, n = 7 ***	72 SD 9, n = 31 ***	NS
<= 50%	0	0	
Ration TrA / DAo (%)	74 SD 9, n = 7 ***	73 SD 11, n = 31 ***	NS
<= 50%	0	0	

** Weight at birth unknown in 5 patients. ** Weight at surgery unknown in 1 patient. *** Only patients with preoperative cardiac catheterization. SD = standard deviation; NS = not significant; FU = follow-up; AoIst = aortic isthmus; DAo = descending aorta; TrA = Distal transverse aortic arch CoAo = Aortic coarctation; d = days; m = months.*

7.4.4 Aortic arch morphology (table 7.4)

Patients with isolated aortic coarctation and aortic coarctation with associated cardiac abnormalities are compared in table 4. An apparent difference in age and

weight at surgery proved not significant. However morphologic arch abnormalities, both of the distal transverse part and the aortic isthmus, are more prominent in patients with aortic coarctation associated with other cardiac abnormalities.

Table 7.4 : Comparison of variables between patients (percentages) with isolated coarctation and coarctation associated with additional cardiac abnormalities.

Variable	Isolated CoAo (n = 9)	Additional Abnormalities (n = 41)	P value
Duration of FU	37m SD 22m	36.2m SD 25.1m	NS
Birth weight (kg)	3.1 SD 0.7, n = 42 *	3.3 SD 0.6 (n = 20)	NS
Age at surgery	76.9d SD 81.6d	43.6d SD 63.5d	NS
Weight at surgery (kg)	4.5 SD 2.0	3.7 SD 1.2, n = 21 **	NS
Ration AoIst / DAo (%)	71 SD 11, n = 34 ***	58 SD 16, n = 18 ***	< 0.01
<= 50%	1 (3)	7 (39)	< 0.01
Ration TrA / DAo (%)	71 SD 13, n = 34 ***	63 SD 11, n = 18 ***	< 0.05
<= 50%	2 (6)	3 (17)	NS
Circumscript CoAo	42 (93)	14 (61)	< 0.01

** Weight at birth unknown in 6 patients. ** Weight at surgery unknown in 6 patients. *** Only patients with preoperative cardiac catheterization. SD = standard deviation; NS = not significant; FU = follow-up; AoIst = aortic isthmus; DAo = descending aorta; TrA = Distal transverse aortic arch; CoAo = Aortic coarctation; d = days; m = months.*

7.5 Discussion

Our results indicate that a substantial proportion of patients operated upon for aortic coarctation of the aorta in their first year of life present with recurrent coarctation (15% in our series) and systolic hypertension (24% in our series) during follow-up. These sequelae already become apparent at young age after relatively short periods of follow-up. Although the occurrence of these sequelae have been emphasized in several reports, to our knowledge this has not been demonstrated for this specific group of patients managed by a single surgical technique in the first year of life.

With respect to the development of recurrent coarctation after successful correction, young age at operation has been identified as an important risk factor [3, 8-10]. In our study group, we confirmed this positive correlation between young age at surgery and coarctation recurrence. However, subsequent regression analysis failed to identify age at operation as relative risk factor but produced weight at surgery and presence of a hypoplastic transverse arch as risk factors. The finding of weight at surgery as risk factor, which is supported by the findings of Brouwer et al. [28], may be related to the age composition of our population. Provided young age at surgery does influence the probability of subsequent development of recurrent coarctation, all our patients were at increased risk, and therefore the presumed influence of age at surgery is not as explicit as in studies that cover patients operated upon at wider age ranges. A similar discrepancy between age at surgery and the development of recurrent stenosis in patients operated at a young age had been demonstrated in previous studies [28, 29]. Our observation that all recoarctations presented during the first postoperative year is consistent with that of authors who have found a similar high incidence of recoarctations in the first postoperative year [30], but also a more gradual development of recurrence over follow-up had been observed [31]. In one of our patients recurrent coarctation was found 35 days after surgical correction. This short interval suggested that the observed recurrence might have been the result of residual coarctation after correction. However, clinical data of this patient proved to be inconclusive in this respect.

Several studies have observed an increase in the incidence of hypertension over follow-up after initial pressure relief. [1-3, 10, 23] A relationship between the development of late hypertension and age at coarctectomy on the one hand [3, 9, 11] and coarctation recurrence on the other hand [8, 10, 22, 23] has frequently been described. Although early repair has been associated with a lower incidence of postoperative hypertension and more voluntary exercise variables at follow-up [22], we found that already 16 out of 68 patients (24%) had developed systolic hypertension after a relatively short period of follow-up. This indicates that even when patients are managed early in life the risk of development of systolic hypertension in the absence of recurrent coarctation is still substantial. These findings are supported by Gardner et al. who demonstrated that persistent functional vascular abnormalities found after repair of coarctation were not related to age at operation, and therefore argued that early repair not necessarily prevents development of vascular abnor-

malities [32]. A similar discrepancy between age at surgery and the presence of systolic hypertension was found by Ong et al [24]. However, in their series of patients with isolated coarctation age at repair was beyond infancy in all cases.

Our observation that late systolic hypertension developed in a substantial proportion of patients without recurrent coarctation, larger than would be expected on normal population variation, indicates that apart from recurrent coarctation other, largely unknown, mechanisms play an important role in the pathogenesis of post coarctectomy hypertension. Various studies have investigated potential pathogenic mechanisms, and abnormalities have been found with respect to left ventricular function [33, 34], baroreceptor function [26, 35], arterial dilatation [32], upper body vascular structure and resistance [25, 35]. Unfortunately, the heterogeneity of the various studies, with respect to population composition, management approach, follow-up duration, and the sometimes controversial outcomes take interpretation of results difficult.

Several authors have reported on the co-occurrence of underdevelopment of various parts of the aortic arch in patients with aortic coarctation especially, but not exclusively [16], in patients with additional structural cardiac abnormalities that require management shortly after birth [12-14]. This underdevelopment usually involves the distal transverse arch (type I hypoplasia according to the definitions of Moulaert et al. [36]). Increased mortality and recurrent coarctation have been associated with untreated or disregarded hypoplasia of the aortic arch [16-19], but others have questioned its role in the development of recurrence of pressure gradients [12,20,21]. An association of aortic arch hypoplasia with additional cardiac anomalies and a correlation with recurrence of coarctation are also found in our series. However, with respect to the development of systolic hypertension no such relation was found. Moreover, almost equal mean rations of both transverse arch and isthmic dimensions and no hypoplasia were found both in patients with and without systolic hypertension in the absence of recurrent coarctation. This makes underdevelopment of the aortic arch as a potential etiologic factor for the development of late systolic hypertension unlikely.

7.5.1 Comments

The use of descending aorta diameters in calculating aortic arch ratios in our study is different from other investigators who used the diameter of the ascending aorta as reference [14, 21, 36] but has been used before [17]. In a number of our patients visualization of the aortic arch was performed by retrograde angiography through the right subclavian artery. Because in these patients no ascending aorta diameter could be measured, and the descending aorta diameter is presumed to be of normal dimension [15], it was adapted as reference for all patients with angiographic data.

7.5.2 Conclusion

Results in our study indicate that both recurrent coarctation and late systolic hypertension constitute a substantial problem affecting 15% and 24% of patients managed for aortic coarctation in the first year of life respectively. A relationship was found between recurrent coarctation and both the presence of systolic hypertension at the end of follow-up, and hypoplasia of the aortic arch. However, a relationship between aortic arch morphology and late systolic hypertension was not found. Systolic hypertension is present in a substantial fraction of patients managed for circumscript lesions in the absence of signs of recurrent coarctation. Therefore, it is argued that other, unknown, determinants play an important role in the development of late hypertension and that their influence is already apparent after short periods of follow-up in patients operated upon at young age.

7.6 References

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Summary

Summary, discussion, and conclusions

8

8.1 Introduction

In Chapter 1 the aim of the thesis is introduced. The central theme of the work presented in this thesis is to apply medical information technology and to show the possible role for the support of follow-up and outcome research in congenital heart disease. The first section, consisting of Chapters 2, 3, and 4 is methodological. The evolution of classification and coding of congenital heart disease is reviewed and the development of an improved domain nomenclature and its implementation in a computer based system is described. In the second section the Chapters 5, 6, and 7 present three clinical studies which were used to present the first experiences with this new nomenclature and the terminology system to support follow-up and evaluation studies necessary for the development of clinical management models.

8.2 Methodology

In Chapter 2 a review is given of past and present developments in the classification and coding of congenital cardiac abnormalities. The first part of this chapter briefly reviews the evolution of the morphologic approach to the description of congenital heart disease. The segmental approach introduced by Van Praagh and co-workers has eventually led to the two main morphologic description methods currently used. Central to this original work was that cardiac malformations can be described as orientational and positional abnormalities of the three main cardiac

segments; atria, ventricles, and great arteries organized in veno-arterial order. The addition of two connecting segments was the most important extension of the original situs description and proved necessary to encompass unusual morphology. Persistent dissatisfaction with the segmental approach has led to an alternative approach by a group of British morphologists led by Anderson. Central to the approach of this "European school" was their emphasis on connexions rather than spatial relationships of the cardiac segments. Shortly after introduction an important change was made. The initial concept of the univentricular heart was shown to be morphologically incorrect and was soon replaced by the univentricular atrioventricular connection. Both the "European" and the "American" school have continued to evolve and are still used in their respective continents of origin.

The second part of Chapter 2 describes the main coding schemes that have been developed on the basis of the two morphologic methods to "code" cardiac abnormalities found in patients in a uniform manner to facilitate case retrieval and identification of study populations. The main problems associated with these schemes are identified and described in terms of their content, organization and suitability for the support of patient care and clinical research. In terms of content they pose the problem that they are solely based on anatomy and lack or only partially cover nomenclature on pathophysiology, (surgical) management and outcome. Organized as "vocabularies" (simple lists) their suitability for both clinically oriented collection of patient data and subsequent retrieval is limited because of their non-clinical organization, lack of control over combinations of terms, and because they are paper-based.

The main conclusion of Chapter 2 is that the structure and contents of traditional coding schemes are unsuitable for the computerized recording of patient data and the subsequent assessment of clinical management in congenital cardiology.

Chapter 3 and 4 describe the rationale behind and the implementation of a new terminology system for the maintenance and use of complex nomenclatures in a highly specialized medical domain such as congenital cardiology. Experience with traditional coding schemes in general medicine and more specialized domains have shown that these schemes are unsuitable for current information requirements. The increase of computerization of medical data and expansion of its use over the last

decade have made these limitations manifest. Especially evaluation of clinical practice and the development of management strategies that are based on retrospective or prospective studies require high quality, detailed descriptions of patient data.

As the main source of limitations of traditional approaches to capturing domain nomenclature in coding schemes, their limited structure for organizing nomenclature items was identified. Many researchers have realized that in order to overcome these limitations and to acquire high quality data it is of fundamental importance to capture the clinical context in which patient data arises, in addition to nomenclature and automated control over the process of data collection. Various approaches to find a solution have been applied which vary widely in aim, methodology, and current stage of development. Currently a major effort is put into the development of terminology systems that are able to capture the richness and detail of the paper medical record. These systems have the highest requirements with respect to the broadness and detail of the nomenclature used. Others focus on more limited domains and abstraction of data in the medical record rather than representing its full contents. Although the applied information representation techniques are diverse, conceptual graphs, semantic networks, or frame-base techniques, central to all is making implicit medical knowledge explicit. Especially efforts to develop medical record systems are in their early stages.

In Chapter 3 the requirements and technical design of our terminology system are described. Central to its design is the requirement for its applicability to both collection of patient data and their subsequent analysis. A semantic network approach was used to structure the nomenclature into a flexible framework. This flexibility is necessary to capture in one terminology system the large differences in presentation and nomenclature detail that are required by the inherently different processes of data collection and retrieval.

We have introduced views to capture the spectrum of morphologic abnormalities, physiologic consequences, available treatment options, and follow-up characteristics that are commonly found in patients that present with a congenital heart disease entity. Integrity rules are built into the terminology to achieve automated control over the correct and complete coding of patient data.

Chapter 4 delineates the principles of the terminology system from a practical medical perspective. The complete nomenclature of Fallot's tetralogy is discussed to illustrate the use of views and integrity rules. The contents of the new terminology system were based on an existing comprehensive, but traditional congenital heart disease nomenclature. We have refined and extended its contents to encompass current insights and developments. An important addition was the inclusion of clinical entities in order to describe congenital cardiac abnormalities from a clinical and pathophysiological point of view.

We conclude the description of our system by arguing that such a terminology system based on the combination of representing nomenclature in explicit clinical entity-based context and the use of rules is valuable to achieve optimal use of a nomenclature in research. It is this use of views and rules as solutions for medical knowledge representation that constitutes the major difference between our work as compared to others.

8.3 Clinical studies to assess the management of congenital heart disease

In Chapters 5, 6, and 7 three clinical studies are presented. In all three studies the patient population consisted of consecutive series which were obtained from our departmental database system. This database system was developed during an era before the start of our work for the support of follow-up research in pediatric cardiology. It utilized a coding system consisting of a vocabulary of terms that provided a reasonable coverage of the congenital cardiac domain. Terms were present for the description of morphology, treatment and residual defects. Also nomenclature was included for the description of additional and associated cardiac and non-cardiac anomalies. Since its introduction the system had been used for the collection of a consecutive series of almost 10.000 patients.

However, attempts to use the patient database for research proved impossible. The main cause of this was the coding system; its lack of structure and strictly anatomic, i.e. non-clinical organization that did not allow making patient selections based on clinical disease entities or specific management approaches. The explicit

knowledge to realize this, especially knowledge on meaningful clinical relationships between terms and term groups, was completely lacking. These problems are not specific for this system, but a characteristic of the applied traditional type of coding scheme, as previously described. Also, suitable tools for the support of database analysis that used the coding system were absent. Retrievals were limited to a single step in which occurrences of codes and not distinct patients were retrieved from the database. The results of such a selection step could not be further restricted or extended. Only single codes or a set of codes selected from a limited collection of predefined sets could be used as the argument of the selection step. Facilities to gather relevant codes from the coding system were absent. Other types of criteria such as demographic data or time-related and follow-up events, could not be utilized.

This consecutive series of patients was regarded of considerable value for performing the studies described in Chapters 5, 6, and 7. To perform such management studies, the information technology necessary to optimally support this had to be developed. These aspects were the main motivations behind the work described in the thesis.

In Chapter 5 the results of a study to assess the predictive impact of morphological, hemodynamic, and clinical variables in the management of patients with isolated ventricular septal defect (VSD) are presented. The need for this study is associated with the persisting controversy in timing of surgical management of patients with non-restrictive, isolated VSD. This controversy is mainly related to the risks of developing pulmonary vascular obstructive disease and the probability of spontaneous closure of the defect. Findings indicated that early surgical closure of non-restrictive VSD is warranted when severe growth delay occurs, or in case of heart failure. In other instances conservative management is justified; the probability of spontaneous closure and the period over which this can be expected being only determined by the morphological type of the defect.

Two main aspects of our approach to the application of information technology for support of clinical research are illustrated by this study. Firstly, for the identification of such study patients a sophisticated and flexible retrieval mechanism is needed. In the setting of this study such a tool is required to be able to distinguish

between those patients with isolated ventricular septal defects and others in which the VSD is part of a complex congenital cardiac abnormality. This tool is also required to identify patients that have "isolated" VSD with co-occurring abnormalities that are regarded as minor, such as small atrial septal defects. Patients with associated lesions that are judged to be irrelevant in this specific research situation, such as chromosomal abnormalities, also need to be included. Secondly, this study clearly illustrates the need for relationships between morphology and physiology when a terminology is intended for clinical application. Not the physical size of the VSD but its pathophysiological effect, the magnitude of left to right ventricular shunting, was found to be relevant for outcome.

Chapter 6 studies the impact of introduction of the balloon dilatation technique on the management regimen of aortic valve stenosis and its subsequent effect on clinical status in patients with non-critical, isolated aortic valve stenosis. In this survey two consecutive groups of patients with similar morphology and comparable duration of follow-up after management are compared. The two groups differ with respect to the management strategy used; surgical valvulotomy in the first group and balloon dilatation in the second. We have found that both treatment regimens are comparable with respect to freedom from re-intervention and residual defects (aortic regurgitation). However, balloon dilatation is performed earlier and at lower transvalvular pressure gradients, keeping the population (residual) gradient at a lower level. It is therefore argued that balloon dilatation is an equally effective alternative to surgical valvulotomy but has the advantage of delaying inevitable future surgery.

This survey illustrates the need for studies which evaluate new or improved management strategies. Preferably such studies should be carried out as randomized, prospective trials but in practice this is often not possible for practical or ethical reasons. In our situation the consecutive nature of the patient database allowed us to make such a comparison retrospectively. The retrieval functionality needed to identify these two historic groups is comparable to that required for the identification of the VSD study group described in Chapter 5. During analysis and comparison of patient data that were retrieved from the database through different approaches, discrepancies emerged. These differences were traced back and found to be the result of inconsistencies and errors in patient codings; inaccurate or incom-

plete morphologic description or correct coding of the treatment event but without specification of underlying morphology. These inconsistencies are a well known problem associated with traditional, uncontrolled coding systems. They obstruct unconstrained and reliable identification of research populations and, when undiscovered, may result in inaccurate or even erroneous outcomes and conclusions.

Our views and integrity rules mechanism has been devised to achieve the high quality data which are needed for clinical studies. This is realized by means of a logical, clinical presentation of items available for coding and by means of implementation of explicit control over the correctness and completeness of what is abstracted. We argue that discrepancies such as encountered in the research setting of Chapter 6 are preventable. A view offers the appropriate nomenclature and rules to ensure their correct use. Coding a balloon valvuloplasty is only allowed when aortic valve outflow obstruction (irrespective of its cause) is present in combination with a specification of severity that warrants intervention.

Chapter 7 presents a third management study. Determinants for recurrent coarctation and systolic hypertension at the end of follow-up were studied in a consecutive group of patients who were treated by surgical resection of aortic coarctation in the first year of life. The controversial relationship between late hypertension and recurrent coarctation on the one hand and the influence of aortic arch morphology on development of these sequelae on the other hand were the background of this study. The presence of systolic hypertension at the end of follow-up and a history of recurrent coarctation are found to be related. However systolic hypertension is also present in a substantial fraction of patients in the absence of recurrent coarctation. Both recurrent coarctation and systolic hypertension at the end of follow-up are not related to coarctation morphology. It is argued that other determinants play an important role in the pathogenesis of systolic hypertension and that their influence becomes already apparent after short periods of follow-up in patients operated upon at a young age.

This study illustrates the need for tools that allow rapid completion of studies to evaluate new approaches to diagnosis and treatment. Early identification of potential long-term complications is important for modification, change or even eradi-

cation of new approaches and return to earlier management regimens that were rendered obsolete.

The three clinical studies presented are our first experiences with an advanced terminology system for the maintenance and use of complex terminology in a highly specialized domain of medicine, congenital heart disease. They show the crucial role of a nomenclature that is comprehensive, maintainable, and that is capable of capturing aspects of morphology and their pathophysiologic consequences as well as aspects of management and follow-up in their clinical context. Because high quality patient data are a fundamental prerequisite for performing research, these knowledge-based techniques should support all stages of the research process; from the collection of patient data to its analysis.

These studies have also shown the important role of a knowledge-based terminology system, such as SmaCS, and flexible query tool in the solution of complex research questions. The query tool allows identification of required study populations in a stepwise, set based, and clinically oriented manner using both coded and non-coded data. The terminology system itself plays a crucial role in the analysis of complex coded patient data, by supporting the selection and gathering of terms which are relevant in the setting of a specific (clinical) research question. It is this combination of the SmaCS query tool and terminology system that has made the described clinical studies possible.

The work in this thesis represents only an initial step towards the use of medical information technology in clinical research. Nevertheless, these experiences show that application of such technology for the support of clinical management studies is feasible. They also show the significance of actual application of such techniques in the clinical setting for (further) development. It is obvious that a collaboration between (medical) domain experts and workers in medical informatics to achieve this is crucial.

Samenvatting, discussie en conclusies

8.1 Inleiding

De doelstelling van het proefschrift wordt geïntroduceerd in Hoofdstuk 1. De toepassing van medische informatica technologie en het demonstreren van de mogenlijke rol hiervan voor de ondersteuning van follow-up en outcome studies op het gebied van aangeboren hartafwijkingen vormen het centrale thema in dit proefschrift. Het eerste deel, gevormd door de Hoofdstukken 2, 3 en 4, is methodologisch. Er wordt een overzicht gegeven van de evolutie van het classificeren en coderen van aangeboren hartafwijkingen. Vervolgens wordt de ontwikkeling van een verbeterde nomenclatuur voor het domein van aangeboren hartafwijkingen en de implementatie hiervan in een computer systeem beschreven. De Hoofdstukken 5, 6 en 7 vormen het tweede deel waarin drie klinische studies worden beschreven. Deze studies geven de eerste ervaringen weer met het gebruik van de nieuwe nomenclatuur en het ontwikkelde terminologiesysteem voor de ondersteuning van follow-up en evaluatiestudies. Dergelijke studies zijn essentieel voor de ontwikkeling van klinische behandelings- of managementmodellen.

8.2 Methodologie

In Hoofdstuk 2 wordt een overzicht gegeven van historische en recente ontwikkelingen in het classificeren en coderen van aangeboren hartafwijkingen. Allereerst wordt in dit Hoofdstuk de evolutie van de morfologische beschrijvingswijze van

aangeboren hartafwijkingen beknopt beschreven. De segmentale benadering, geïntroduceerd door Van Praagh en medewerkers, heeft uiteindelijk geresulteerd in de twee belangrijkste beschrijvingsmethoden die momenteel worden gebruikt, de "Amerikaanse" en de "Europese" school. De kern van dit werk is een beschrijvingsmethode waarbij structurele hartafwijkingen weergegeven werden als afwijkingen in de oriëntatie en positie van de drie belangrijkste segmenten van het hart: atria, ventrikels, en grote arteriën gerangschikt in veneus arteriële volgorde. De toevoeging van twee verbindingssegmenten vormde de belangrijkste uitbreiding van deze beschrijvingsmethode en was noodzakelijk om beschrijving van bijzondere morfologie mogelijk te maken. Ontevredenheid met deze segmentale benadering heeft geleid tot een alternatieve benadering ontwikkeld door een groep Britse morfologen onder leiding van Anderson. Centraal in de benadering van deze "Europese school" is hun nadruk op connecties tussen de cardiale segmenten in plaats van ruimtelijke relaties. Kort na de introductie werd ook in hun benadering een belangrijke aanpassing gemaakt. Het initiële idee van het univentriculaire hart bleek morfologisch incorrect en werd vervangen door de univentriculaire atrioventriculaire connectie. Zowel de benadering van de "Europese" als van de "Amerikaanse" school zijn verder geëvolueerd en worden beiden gebruikt in hun respectievelijke continent van oorsprong.

In het tweede deel van Hoofdstuk 2 worden de belangrijkste coderingsschema's besproken die ontwikkeld zijn op basis van de twee morfologische beschrijvingsmethoden. Het doel van deze schema's is het op uniforme wijze "coderen" van hartafwijkingen, teneinde individuele gevallen en onderzoekspopulaties te kunnen identificeren. De belangrijkste problemen, die gerelateerd zijn aan het gebruik van deze schema's, worden geïdentificeerd en beschreven in termen van inhoud, organisatie en geschiktheid voor de ondersteuning van patiëntenzorg en klinisch wetenschappelijk onderzoek. Inhoudelijke beperkingen komen voort uit het vrijwel uitsluitend op anatomie gebaseerd zijn en het geheel of gedeeltelijk ontbreken van nomenclatuur met betrekking tot pathofysiologie, (chirurgische) behandeling en behandelingsresultaat. Geschiktheid voor zowel een klinisch georiënteerde verzameling van patiëntengegevens als voor extractie van verzamelde gegevens wordt verder beperkt door hun organisatie als lexicons (eenvoudige lijsten). Een niet klinische presentatie van termen en het ontbreken van controle over combinaties van

geselecteerde termen zijn de belangrijkste beperkingen van dergelijke coderingsschema's.

De belangrijkste conclusie van Hoofdstuk 2 is dat de inhoud en structuur van traditionele coderingsschema's ontoereikend is voor computer ondersteunde registratie van patiëntengegevens en voor ontwikkeling van klinische behandelingsstrategieën op het gebied van congenitale hartafwijkingen.

De hoofdstukken 3 en 4 beschrijven de onderliggende principes en de implementatie van een nieuw terminologiesysteem voor de ontwikkeling, onderhoud en het gebruik van complexe nomenclaturen in gespecialiseerde medische domeinen zoals de congenitale cardiologie. Ervaringen met het gebruik van traditionele coderingsschema's in zowel de algemene geneeskunde als in meer gespecialiseerde domeinen heeft aangetoond dat dergelijke schema's niet geschikt zijn voor de huidige informatiebehoeften. De over de laatste jaren toegenomen automatisering van medische gegevens en de verbreding van het gebruik van deze gegevens hebben deze beperkingen duidelijk gemaakt. Met name evaluatie van het medisch handelen en de ontwikkeling van behandelingsstrategieën, gebaseerd op gegevens uit retrospectieve of prospectieve studies, vereisen gedetailleerde en nauwkeurige patiëntbeschrijvingen.

De beperkte structuur voor de organisatie van de afzonderlijke termen in een nomenclatuur blijkt de belangrijkste beperkende factor in traditionele coderingsschema's. Verschillende studies hebben uitgewezen dat het van fundamentel belang is de klinische context waarin de gegevens ontstaan in het gegevensverzamelingsproces te betrekken, om aan deze beperkingen tegemoet te komen en gegevens van hoge kwaliteit te verkrijgen. Voorwaarden hiervoor zijn de beschikbaarheid van de juiste nomenclatuur en de aanwezigheid van controle over het gegevensverzamelingsproces. Teneinde een dergelijke terminologie te realiseren zijn verschillende onderzoeksbenaderingen gevolgd die onderling sterk verschillen in doelstelling, gebruikte methodologie en huidige stand van ontwikkeling. Momenteel zijn veel inspanningen gericht op de ontwikkeling van terminologie systemen die in staat zijn de breedheid en detaillering van het papieren medische dossier vast te leggen. Dergelijke systemen stellen de hoogste eisen voor wat betreft de benodigde nomenclatuur. Anderen richten zich in hun onderzoek op beperktere domei-

nen en op abstractie van relevante gegevens uit het medische dossier in plaats van representatie van de volledige inhoud. Hoewel de toegepaste technieken sterk uiteenlopen hebben zij het expliciteren van impliciete medische kennis gemeenschappelijk. Met name de ontwikkelingen die zich richten op medische dossier systemen bevinden zich in de beginfase.

In Hoofdstuk 3 worden de criteria en het technisch ontwerp van het door ons ontwikkelde terminologie systeem beschreven. Centraal in het ontwerp is de geschiktheid van het terminologie systeem voor zowel verzameling van patiëntengegevens als voor het gebruik van de verzamelde gegevens in de hierop volgende analyse. Er is gekozen voor een semantisch netwerk om een bestaande nomenclatuur op het gebied van aangeboren hartafwijkingen in een flexibel raamwerk te kunnen structureren. Deze flexibiliteit is nodig om de grote verschillen in presentatie en detaillering van termen, die nodig zijn voor gegevensverzameling en gegevens analyse, in één terminologie systeem te kunnen verenigen.

Aan het terminologiesysteem zijn een view- en een integriteitscontrole- mechanisme toegevoegd. Views zijn geïntroduceerd om klinische entiteiten van aangeboren hartafwijkingen te kunnen representeren. Binnen dergelijke views worden slechts die onderdelen uit het spectrum van morfologische afwijkingen, de hieraan gerelateerde fysiologische consequenties, de beschikbare behandelingsopties en follow-up karakteristieken, gerepresenteerd welke gevonden kunnen worden binnen een gegeven entiteit. Integriteitscontroles zijn toegevoegd om, middels automatische controle, de juistheid en compleetheid van de verzamelde gegevens te kunnen bewaken en verbeteren.

De inhoud van het nieuwe terminologiesysteem is gebaseerd op een bestaand relatief compleet, maar volgens traditionele principes opgebouwd coderingsschema van aangeboren hartafwijkingen. De inhoud hiervan is op basis van de huidige inzichten en ontwikkelingen uitgebreid en verfijnd. Een belangrijke toevoeging bestond uit de introductie van een aantal klinische entiteiten waarin veel voorkomende aangeboren hartafwijkingen zijn beschreven vanuit een klinisch, pathofysiologisch standpunt.

Hoofdstuk 4 beschrijft de principes van het terminologie systeem vanuit een praktisch medisch standpunt. De complete nomenclatuur van de entiteit "tetralogie van Fallot" wordt gebruikt om het view- en integriteitscontrole- principe te illustreren.

De beschrijving van het terminologiesysteem wordt afgesloten met de hypothese dat een dergelijk, sterk op de klinische praktijk gericht terminologiesysteem, een belangrijke stap vormt in de richting van een optimale afstemming van een nomenclatuur op het gebruik in klinisch wetenschappelijk onderzoek. Ons gebruik van views en integriteitscontroles vormt het belangrijkste verschil tussen ons werk en het werk van andere onderzoekers op het gebied van medische kennisrepresentatie.

8.3 Klinische studies voor de bepaling van behandelingsstrategieën voor aangeboren hartafwijkingen

In de Hoofdstukken 5, 6 en 7 worden 3 klinische studies gepresenteerd. In deze drie studies bestond de patiëntenpopulatie uit een in de tijd aaneengesloten serie patiënten, afkomstig uit ons afdelings informatiesysteem, maar geïdentificeerd middels het ontwikkelde nieuwe terminologie systeem. Dit afdelings informatiesysteem is destijds specifiek voor de ondersteuning van vervolgonderzoek op het gebied van de kindercardiologie ontwikkeld. Voor het coderen van patiënten was een coderingssysteem beschikbaar dat bestond uit een lexicon van termen waarmee een acceptabele dekking van het aangeboren hartafwijkingen domein werd verkregen. Termen waren aanwezig voor de beschrijving van zowel morfologie als van behandeling en eventuele restafwijkingen. Daarnaast was ook voorzien in nomenclatuur voor de beschrijving van additionele en geassocieerd cardiale en niet-cardiale afwijkingen. Vanaf de introductie is het systeem gebruikt voor de verzameling van bijna 10.000 patiënten.

Het bleek echter niet mogelijk de gegevensbestanden te gebruiken voor onderzoek. De belangrijkste oorzaak hiervan was het coderingssysteem, waarin een gebrek aan structuur en een strikt anatomische, niet-klinische organisatie van de nomenclatuur items het niet mogelijk maakten patiënten te selecteren op basis van klinische enti-

teiten of specifieke behandelingen. Expliciet medische kennis, in het bijzonder kennis over relevante klinische relaties tussen termen en groepen van termen, ontbrak volledig in het coderingssysteem. Deze problemen zijn niet specifiek voor dit systeem, maar een eigenschap van het toegepaste "traditionele" type coderingssysteem, zoals eerder beschreven. Ook ontbraken de noodzakelijke hulpmiddelen voor de ondersteuning van het gebruik van dit coderingssysteem bij de analyse van de gegevensbestanden. Extracties waren beperkt tot enkelvoudige stappen waarbij coderingen en niet afzonderlijke patiënten uit de gegevensbestanden werden opgehaald. De resultaten van deze enkelvoudige stappen konden bovendien niet verder worden geanalyseerd. Alleen enkelvoudige coderingen of een set coderingen, gekozen uit een beperkte verzameling van voorgedefinieerde sets, konden worden gebruikt als argument van een selectiestap. Het was niet mogelijk relevante coderingen middels het coderingssysteem te verzamelen. Andere typen argumenten zoals demografische of tijdsgerelateerde gegevens konden niet ten bate worden gemaakt.

Deze opeenvolgende serie patiënten werd echter beschouwd als uiterst waardevol voor het uitvoeren van studies zoals beschreven in de Hoofdstukken 5, 6 en 7. Om dergelijke studies naar behandelingsstrategieën te kunnen uitvoeren, was het noodzakelijk, technologie te ontwikkelen, die voor optimale ondersteuning van dit onderzoek kon zorgdragen.

In Hoofdstuk 5 worden de resultaten gepresenteerd van een studie die tot doel had de predictieve waarde van morfologische, hemodynamische en klinische variabelen voor de behandeling van patiënten met geïsoleerd ventrikelseptum defect (VSD) vast te stellen. De noodzaak van deze studie is gerelateerd aan de voortdurende controverse in de bepaling van het optimale tijdstip van chirurgische behandeling in patiënten met niet drukscheidend, geïsoleerd VSD. Deze controverse is voornamelijk de resultante van het risico op ontwikkeling van pulmonaalvasculair obstructieve afwijkingen enerzijds en de waarschijnlijkheid van spontane sluiting van het defect anderzijds. De bevindingen gaven aan dat vroegtijdige sluiting van niet drukscheidend VSD geïndiceerd is wanneer ernstige groeivertraging optreedt, of wanneer er sprake is van hartfalen. In andere situaties is niet-chirurgische behandeling verantwoord. De waarschijnlijkheid van spontane sluiting en de periode

waarover dit kan worden verwacht bleken alleen bepaald te zijn door het morfologische type van het defect.

Deze studie illustreert twee hoofdaspecten van onze benadering van toegepaste informatietechnologie ter ondersteuning van klinisch onderzoek. In de eerste plaats is voor de identificatie van een dergelijke studiepopulatie een flexibele gegevensanalyse module nodig. In deze studie is een dergelijk hulpmiddel nodig om een onderscheid te kunnen maken tussen patiënten met een geïsoleerd ventrikelseptum defect en patiënten waarin het VSD deel uitmaakt van een complexe congenitale hartafwijking. Ook is een dergelijk hulpmiddel nodig om patiënten te identificeren die een "geïsoleerd" VSD hebben in combinatie met andere afwijkingen die, in deze situatie, als onbelangrijk kunnen worden beschouwd, zoals een klein atriumseptum defect. Ook de patiënten met geassocieerde, niet cardiale afwijkingen die voor de specifieke onderzoekssituatie als onbelangrijk kunnen worden beschouwd dienen in de onderzoekspopulatie te worden meegenomen. Patiënten met een VSD en een chromosoomafwijking zijn hier een voorbeeld van. In de tweede plaats geeft deze studie duidelijk de noodzaak aan van het aanbrengen van verbanden tussen morfologie en fysiologie: niet de fysieke afmeting van het VSD, maar het pathofysiologisch effect, de grootte van de links-rechts bloedstroom, bleek een relevante factor te zijn in de uiteindelijke behandelingsuitkomst.

In Hoofdstuk 6 wordt het belang van de introductie van de ballondilatatie techniek voor de behandeling van niet-kritische, geïsoleerde aortaklep stenose en het effect van het behandelingsregime op de klinische toestand van patiënten bestudeerd. In deze studie worden twee patiëntengroepen met elkaar vergeleken, die voor wat betreft de onderliggende morfologische afwijking en duur van vervolging na de behandeling vergelijkbaar zijn. Beide groepen verschillen van elkaar voor wat betreft het toegepaste behandelingsregime: chirurgische valvulotomie in de eerste groep en ballondilatatie in de tweede. Onze bevindingen geven aan dat beide behandelingsregimes vergelijkbaar zijn voor wat betreft herbehandelings vrije periode en restafwijkingen (aortaklep insufficiëntie). Ballondilatatie wordt echter eerder toegepast en bij lagere klepgradiënten waardoor de (rest) klepgradiënt over het algemeen op een lager niveau wordt gehouden. Op basis hiervan wordt beargumenteerd dat ballondilatatie een goede alternatieve methode voor chirurgische be-

handeling is met een vergelijkbare efficiëntie, maar met het voordeel dat het het op termijn onvermijdelijk chirurgisch ingrijpen kan uitstellen.

Dit onderzoek illustreert de noodzaak van studies voor de evaluatie van nieuwe of verbeterde behandelingsregimes. Hoewel dergelijke studies bij voorkeur uitgevoerd dienen te worden als gerandomiseerde prospectieve studies, is dit in de praktijk niet altijd mogelijk, om praktische en ethische redenen. In onze situatie bood het aaneengesloten karakter van de patiënten gegevensverzameling de mogelijkheid een dergelijke vergelijking retrospectief te maken. De gegevensanalyse functionaliteit, gebruikt voor de identificatie van de twee historische groepen, is vergelijkbaar met die voor de identificatie van de VSD studiegroep zoals beschreven in Hoofdstuk 5. Tijdens de analyse en de vergelijking van patiëntengroepen, die op verschillende manieren uit het gegevensbestand waren selecteerd, kwamen verschillen naar voren. Deze verschillen werden teruggevoerd op fouten en inconsistenties in de coderingen van patiënten. Voorbeelden hiervan zijn onnauwkeurige en onvolledige morfologische beschrijvingen en correcte beschrijvingen van behandeling in de afwezigheid van codering. Dergelijke inconsistenties zijn een bekend probleem en inherent aan de traditionele, ongecontroleerde coderingssystemen. Zij bemoeilijken onbeperkte identificatie van onderzoekspopulaties en kunnen, indien niet onderkend, tot onnauwkeurige of zelfs foutieve uitkomsten en conclusies leiden.

Ons mechanisme van views en integriteitscontroles is ontwikkeld om een hoge kwaliteit van gegevens, nodig voor de uitvoering van klinische studies, te verkrijgen. Dit wordt enerzijds gerealiseerd middels een logische, klinische presentatie van voor codering beschikbare items en anderzijds middels toepassing van expliciete controle over de juistheid en compleetheid van datgene wat wordt gecodeerd. Wij menen dat op een dergelijke manier discrepanties, zoals deze zich voordeden in de onderzoekssituatie in Hoofdstuk 6, zijn te voorkomen. Een view biedt de juiste nomenclatuur aan en de integriteitscontroles verzekeren het juiste gebruik. Het coderen van een ballooninterventie is in een dergelijke situatie alleen toegestaan wanneer een aortaklep uitstroomobstructie (los van de oorzaak) van dusdanige ernst aanwezig is, dat ingrijpen is geïndiceerd.

In Hoofdstuk 7 wordt een derde management studie gepresenteerd. Determinanten van re-coarctatie en systolische hypertensie aan het einde van follow-up werden bestudeerd in een groep patiënten welke in het eerste levensjaar middels chirurgische coarctatie resectie werden behandeld. De controversiële relatie tussen late hypertensie en recidiverende coarctatie en de invloed van aortaboog morfologie op het ontstaan van deze "complicaties" vormden de achtergrond van deze studie. Er werd een relatie gevonden tussen systolische hypertensie aan het einde van follow-up en een voorgeschiedenis van recidiverende coarctatie. Zowel recidiverende coarctatie als systolische hypertensie aan het einde van follow-up waren niet aan coarctatie morfologie gerelateerd. Er is beargumenteerd dat andere determinanten een belangrijke rol moeten spelen in het ontstaan van late systolische hypertensie en dat de invloed van deze factoren zich al manifesteert na korte vervolgingsperioden bij patiënten die op jonge leeftijd zijn geopereerd.

Deze studie illustreert de noodzaak van hulpmiddelen die een snelle evaluatie van nieuwe of verbeterde diagnostische en behandelingsmodaliteiten mogelijk maken. Vroege identificatie van potentiële langetermijn complicaties is belangrijk voor modificatie, verandering of zelfs het verlaten van nieuwe behandelingsregimes en terugkeer naar behandelingsregimes die eerder als verouderd waren beschouwd.

De drie gepresenteerde klinische studies zijn het resultaat van onze eerste ervaringen met een geavanceerd terminologie systeem voor het gebruik van complexe nomenclaturen in een specialistisch domein van de geneeskunde. Zij geven het belang aan van een nomenclatuur die compleet en onderhoudbaar is en de mogelijkheid biedt, naast aspecten van behandeling en follow-up, aspecten van morfologie en pathofysiologie in een klinische context te plaatsen. Omdat patiënten gegevens van hoge kwaliteit een fundamentele voorwaarde zijn voor de uitvoering van onderzoek, dienen deze technieken alle stadia van het onderzoeksproces te ondersteunen, vanaf de verzameling van gegevens tot aan de analyse hiervan.

Deze studies geven ook aan dat een kennis-gebaseerd terminologie systeem als SmaCS en een flexibele analyse module een belangrijke rol kunnen spelen in het oplossen van complexe onderzoeksvragen. De analyse module stelt de onderzoeker in staat de gevraagde studiepopulatie te identificeren op een stapsgewijze, op sets gebaseerde en klinisch georiënteerde manier. Het terminologie systeem zelf speelt

een cruciale rol in de analyse van complexe gecodeerde patiëntengegevens door de selectie van termen, die relevant zijn in de context van een specifieke (klinische) onderzoeksvraag, mogelijk te maken. Deze combinatie van analyse module en terminologie systeem in SmaCS heeft de uitvoering van dergelijke klinische studies op een snelle en verantwoorde manier mogelijk gemaakt.

Het onderzoek, zoals beschreven in dit proefschrift, vormt slechts een initiële stap in de richting van het gebruik van geavanceerde medische informatica technologieën in de context van klinisch wetenschappelijk onderzoek. Desalniettemin geven deze ervaringen aan dat een dergelijk gebruik van medische informatica technologie realiseerbaar en waardevol is. Zij geven ook aan dat praktische toepassing in de klinische omgeving noodzakelijk is voor verdere ontwikkeling ervan. Het spreekt voor zich, dat een nauwe samenwerking tussen medische domein experts en zij die aktief zijn op het gebied van de medische informatica hierbij cruciaal is.

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