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Patients' and physicians' needs, experiences and preferences in the treatment of right ventricular outflow tract dysfunction

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ABSTRACT

BACKGROUND: patients with congenital heart defects, developing right ventricular outflow tract (RVOT) dysfunction, can face repeated open chest interventions over their lifetime. Repeating surgery increases difficulties and procedural risks, and exposes patients to burdensome and long recovery times that may induce them to postpone the treatment, with possible severe and irreversible consequences for their health. The percutaneous procedure was introduced to delay the need for open chest surgery. Uncertainties still exist regarding the lifelong consequences that may result from adopting different treatment strategies. Current decisions on treatment depend on patients' clinical needs, but also on physicians' experience and opinion, patients' preferences, and procedural costs. The objective is to identify which treatment characteristics influence decisions on how to treat patients with RVOT dysfunction.

METHODS: a literature review was conducted, followed by a discussion with a panel of experts. Ten treatment characteristics, potentially relevant for treatment, were identified and rated in a survey, according to the importance assigned to each characteristic by specialist physicians, patients and/or their caregivers.

RESULTS: while some characteristics appear to be more important (risk of severe complications associated with intervention delays) or less important (scar) to both physicians and patients/caregivers, other characteristics are rated differently in importance depending on subjects consulted, e.g., risk of complications during the months post intervention was among the most important characteristics for patients/caregivers, but the fifth most important characteristic for physicians.

CONCLUSIONS: to optimize benefits and efficiency of the treatment strategies, perceptions and opinions from the different subjects involved, together with patients' clinical needs and overall costs, should be considered in decision-making.

Key words: Right ventricular outflow tract dysfunction, Cost benefit, Treatment choice, Preferences

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INTRODUCTION

Right ventricular outflow tract (RVOT) dysfunction is a common and challenging condition in children and adults with congenital heart disease (CHD). CHD affects 0.8% of people at birth (1, 2), who typically appear as "blue babies".

While, in the past, many of these patients died after a few years or even months from birth, advances in surgical treatment for CHD over the last five decades have led to an important increase in life expectancy: 85-90% of patients now can expect to reach adulthood (2, 3). However, as a result, there is an increasing prevalence of patients that must cope with their lifelong condition and related consequences (4-11), one of the most challenging being the development of a dysfunction of the right ventricular outflow tract (RVOT): a deterioration of the bioprosthetic valve (12-16) caused by calcification, intimal proliferation, or graft degeneration, which can cause stenosis and pulmonary regurgitation, either alone or in combination. The stenosis places an increased hemodynamic burden on the right ventricle, and can result in reduced cardiac function (4, 8, 17-24). Long-term observation has revealed the detrimental effect of pulmonary regurgitation on right and left ventricular function (25, 26) and consequently on exercise tolerance (27), as well as producing arrhythmias and an increased risk of sudden death (21, 28-37). Additional issues, like patients' growth, infections and conduit incompetence can also cause the need for a surgical substitution of the valve.

Some decades ago, open heart surgical treatment was implemented to replace the damaged pulmonary valve in patients with RVOT dysfunction. Performed when they develop RVOT dysfunction, surgical procedures give these patients the opportunity to face their condition during their life (38-40). A less invasive, non-surgical procedure, based on implanting a percutaneous pulmonary valve (PPV), was introduced in clinical practice almost 10 years ago (41), with the main objective of reducing the life-time number of open chest surgeries.

Several different issues are nowadays involved in the process of deciding how and when to treat CHD patients developing RVOT dysfunction, with the aim of reaching the best compromise between benefits and costs (both in terms of clinical risks, poor wellbeing, health care resources, loss of productivity) related to the total number of interventions during a patients' life-time. Knowing all these issues is crucial, in order to understand how the different factors can influence the choice of procedure, and it still remains difficult to guide decision making associated to this. This study was performed with the aim of identifying which factors are currently relevant in the decision making process for the treatment of patients with RVOT dysfunction.

METHODS

The work was conducted in three steps. In the first step a literature research was performed. To conduct the review we analyzed papers, reports and any other documents in the English language, that focused on the management of RVOT dysfunction, which were available up to February 2009 from some international databases (such as Medline and Embase). In addition, we also examined the experiences of the clinicians participating in the project. Our objective was to pool information that could help to draft a list of treatment characteristics that were identified as potentially interesting for the target individuals. For the selection of the literature, the English language was chosen for practical reasons, after ascertaining that this criterion was not discriminative of the documents dealing with the topic of interest. Of the 150 documents found, we selected 90 where aspects, that could currently be potentially relevant in deciding how to treat target patients, were dealt with.

In the second step, the results of the literature research were discussed within a panel of experts, which included one physician who was an expert in the management of patients with RVOT dysfunction and one expert in health technology assessment: a list of different characteristics that could be potentially considered when treating patients with this condition was created.

This list of treatment characteristics was surveyed in a study involving four or five physicians who were experts in the management of patients with RVOT dysfunction and four or five patients, or their parents or guardians (in case of patients aged less than 18 years). The patients/caregivers were enrolled among those participating in the survey through their physicians.

The survey was conducted between the end of February and early March 2009 and involved respondents from Italy and Germany. The participants were asked to self-complete an ad hoc prepared questionnaire, where the

list of treatment characteristics was reported. Each characteristic was included in a question asking "how important is the…?" followed by the specification of the characteristic. Beside each question was a horizontal, 10 cm long visual analogue scale, where respondents rated from 0 (corresponding to not important at all) to 10 (corresponding to very important) the corresponding question about the characteristic. The respondent was asked to mark the scale at the point corresponding to the level of importance assigned to each characteristic, according to his/her own opinion. Patients, or their caregivers, were also asked to report some information about patients' age, type of treatment received in the past, and if they were expecting to receive any treatment in the future, and what type of treatment it was. Regarding the physicians, they were also asked to report some information and/or opinions about the current reasons that had determined, in their clinical expert opinion, the choices between the available treatment strategies and which possible consequences could have resulted from these choices.

The survey was conducted in agreement with the National Regulatory Requirements, International Conference on Harmonization Guidelines for Good Clinical Practice and the 18th World Medical Assembly (42) and all subsequent amendments. The Ethical Committee, of the hospital, where the patients or caregivers were involved, was informed about the study, in agreement with current rules. The participants gave their informed consent to take part in the study.

An unrestricted grant was provided by Medtronic to cover logistic and procedural costs for the conduction of the study. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing and publishing the paper.

RESULTS

Literature research

It emerges that several important issues need to be considered and prioritized with the objective of optimizing the benefits of lifelong treatment for the management of patients with RVOT dysfunction.

On the one hand, it was observed that the restoration of pulmonary valve competence at an appropriate time is crucial to improving right ventricular function, to reducing the incidence of arrhythmias, and to improving exercise tolerance (43). In order to preserve right ventricular function (44-47), there is, currently, some inclination to insert a competent valve at an earlier stage: in a recent study by Frigiola et al. (47) it was shown that normalization of ventilatory response to carbon dioxide production is most likely to occur when surgery is performed before the age of 17 years. Furthermore, one can, nowadays, consider to replace the valve a younger age, thanks also to the recent developments in modern operative methods and postoperative care, (16, 48) and to the availability of less invasive percutaneous approaches (49).

On the other hand, surgery is highly invasive and associated with substantial risks: patients often need to stay in intensive care units and to undergo a cardio pulmonary bypass, which can increase morbidity due to clotting, non- optimal organ perfusion, and systemic insult (50). The recovery time is long and could be burdensome to patients (51). Moreover, a number of conduits actually do not work well because of the shape they take once implanted (52).

In addition, patients can require more interventions during their lifespan: in a mixed group of 3017 patients, it was observed that the 10-year survival-probability was 66%, with a mean reoperation-free interval for conduit exchange of 16 years for allografts and 10.3 years for xenografts (53). According to other sources, freedom from replacement of homograft and xenograft conduits ranges from 68% to 95% at 5 years, and 0% to 59% at 10 years (13, 54-60). In a strategy of periodical surgical interventions, every sternotomy and conduit/valve replacement re-exposes patients to additional morbidity and mortality, and becomes technically more challenging for the surgical team because of previous scarring. In a French case-control study (61) it was found that deep wound infection after sternotomy is responsible for doubling mortality rates and the duration of hospital stay, with a median 23 day prolongation of stay.

Besides clinical problems, patients' wellbeing could be significantly impaired (62). Interventions usually have a significant impact on all quality of life dimensions, especially those measuring physical aspects, depression, pain and worries (63, 64). Even coping with the awareness of the potential high risk of mortality and morbidity, particularly when the longevity of the new conduit does not guarantee freedom from future

operations, can negatively influence quality of life of involved individuals (3, 65, 66). Furthermore, surgery is costly, as both the procedure and the follow up management require huge health care resources (67), while consequences related to the clinical implications of the procedure can affect patients', and also their caregivers', ability to return to their normal daily life activities, like working and participating in school or social activities, for an extended period of time (68, 69).

The expectancy of a re-intervention is generally not well accepted and patients can be reluctant to have re-operations, which may induce them, or even their doctors, to postpone the next operation. This increases the risk of irreversible damage to right ventricular myocardial function, with possible health related and life threatening consequences. As a consequence, actual timing of an operation is often biased by the reluctance to commit multiple open heart surgeries, and exposes the right ventricle to an increasing duration of abnormal loading conditions, with possible severe and irreversible consequences on patients' health (44, 48, 70-72). This scenario makes the issue of timing of surgery crucial and unclear (73-75) which poses the important dilemma for clinicians on when to operate patients with RVOT dysfunction.

With the objective of appropriately postponing open heart surgery, some less invasive options have been introduced into clinical practice, like balloon angioplasty or stent implantation within the conduit (76-78). However, these procedures compromise valve function (79-82). A major drawback of bare stenting is that it increases regurgitation (83), which is present in the majority of patients with conduit stenosis, and can have detrimental effect on right ventricular function and risk of arrhythmia (19, 21, 31). Patients with predominant pulmonary regurgitation, or mixed stenosis and pulmonary regurgitation, cannot be adequately treated with stents and may even worsen regurgitation, which may compromise long-term right ventricular function (84). In 2000, the transcatheter valve insertion in the pulmonary position was introduced in clinical practice (41). This option has been shown to be a safe and feasible treatment for both pulmonary stenosis and regurgitation (41, 85-87) and a relatively high number of PPV procedures have been applied in clinical practice (84, 85, 87).

For instance, Lurz and colleagues (49) have recently published results of treatments with PPV performed between 2000 and 2007 in 155 patients with stenosis and/or regurgitation: PPV implantation allowed patients to avoid surgical RVOT revision in the majority of cases, with a freedom from reoperation of 93%, 86%, 84% and 70% at 10, 30, 50 and 70 months, respectively. This was achieved with a very low complication and mortality rate, and the hemodynamic improvement was sustained in the majority of patients, during a follow-up period of a median of 28.4 months.

In a more recent work addressing the current approaches to RVOT dysfunction, Frigiola and colleagues (47) analysed data of patients undergoing surgical pulmonary valve replacement for severe or predominant pulmonary regurgitation. There was a significant reduction in right ventricular volumes and an improvement in right ventricular function, suggesting that, depending on the characteristics of patients, the surgical and the percutaneous technique can be complementary to each other, as the PPV procedure can help to postpone the need for surgery, when appropriate, and might consequently reduce the total number of operations needed across the total lifetime of patients.

However, the issue of durability of pulmonary valve substitutes also applies to the percutaneous valve which is, in fact, susceptible to degeneration and calcification (88). Furthermore, a risk of early device failure has been detected in a number of cases (89, 90), which could require patients to repeat the procedure within a relatively short term. In addition, the risk of acute complications could require even emergency rescue surgery.

Regarding the first point, Nordmeyer and co. (90) have reported the results of repeat PPV implantations performed in 20 out of 173 (11.6%) patients between 2000 and 2007. The reasons why the procedure had to be repeated were attributable to right ventricular hypertension due to RVOT obstruction caused by early device failure. PPV procedure could be repeated in all the patients, with no procedural complications. Four out of the 20 patients required a third procedure, one was waiting for an open heart surgical procedure, while the others did not require further intervention and had improved haemodynamics in a mean follow-up of around 11 months.

Regarding acute complications, which may potentially lead to emergency rescue surgery (ERS), Kostolny and co. (91) reviewed the occurrence of complications requiring emergency rescue surgery in 6 out of 152 patients who had undergone PPV, during 7 years of observation for the following reasons: dislodgement into a dilated right ventricular outflow tract, acute left heart failure as a result of a compression of the

left coronary artery, and ruptured homograft with massive haemorrhage. The results suggested that some of the acute complications of PPV were probably related to a learning curve, though the authors underlined that the need for emergency rescue surgery is unlikely to be completely abolished. However, ten years of observations is too short a period and it does not consent a full understanding of all the advantages and disadvantages of the possible surgical options.

Finally, the cost of the device could contribute to increase the procedural costs, although a possible reduction of other costs can be expected (e.g. no need to stay in intensive care unit, reduced length of hospital stay, quicker recovery time) (86, 90, 92).

Experts discussion

After discussing the issues found in literature, the following ten characteristics were identified as potentially relevant when treating patients with RVOT dysfunction and we suggest they be considered during decision-making processes: 1) risk of major procedural complications, which may lead to repeating the intervention, to emergency rescue surgery, or even to death; 2) risk of complications occurring during the initial months after the intervention (like early device degeneration, endocarditis, stent fracture, ventricular tachycardia, compression of the valve by the sternum) and which require medical care, hospitalization or even a repetition of the intervention; 3) dimension and position of the scar; 4) perception of pain after the intervention; 5) length and type of hospital stay (for instance at intensive care unit) required to perform the intervention as well as post-operative assistance required; 6) time necessary to return to normal daily life activities, like going to work (including that of the parent taking care of the patient) or to school, doing leisure activities, sport, staying with friends and other people; 7) length of time (years) elapsing until the intervention has to be repeated; 8) risk of complications that can be attributable to intervention delay, like heart failure, arrhythmia, or sudden death; 9) perception of fear for the successive intervention; 10) cost of performing the intervention: tests and examinations (e.g. chest X-ray, echocardiogram, MRI), instruments and equipment, anaesthesia, drugs, procedure/operative time, cost of intensive care, cost of hospital stay.

Survey

Nine people from Germany and Italy participated in the survey: two adult patients (45 and 27 years old), the caregivers of two paediatric patients aged 15 and 16 years, and five physicians (3 cardiologists and 2 surgeons).

Regarding the patients, at the time of the interview two patients had undergone two interventions each, one surgical and one percutaneous, while three patients had undergone one intervention each: one patient had undergone surgery and two patients a percutaneous intervention.

The physicians reported that a patient can undergo on average 3 to 5 open heart interventions during his life. They also specified that there is a causal relationship between the execution of repeated open heart interventions and an increased risk of morbidity for the patients. Four of these physicians stated that even a higher risk of mortality is causally related to repeated open heart surgeries. The level of importance assigned to this relationship was on average 8.7 (min=7, max=10). Three physicians affirmed that the main reasons why surgical interventions are postponed is the reluctance on the part of the patient or his family caregiver (e.g., parent) to undergo another surgery, the risk of surgical and/or post-surgical complications (two of them), and the difficulty of performing the procedure itself (two physicians). Furthermore, one physician stated that it could also be the physician's low ability to convince the patient of the need of re-operation without delaying it too much, while another doctor specified that only urgent interventions could not be postponed.

Regarding the main reasons that emerged for choosing the percutaneous procedure to be applied instead of the traditional intervention to treat RVOT patients, the physicians reported: their intention to limit the risk of surgical/post-surgical complications (five physicians) and the difficulty of performing the traditional intervention (two physicians). In particular, it was specified that the traditional intervention can seldom be performed in the presence of heart failure, and that, after the 4-5th intervention, surgery is no longer practicable. A further possible reason why the percutaneous procedure is performed is the intention of physicians to reduce the length of hospital stay, the risk of staying in Intensive Care Units, and the time necessary for the patient to return to normal activities (three physicians). The reduction of patients' overall discomfort

(one physician), the reluctance of the patients and/or caregiver to undergo another open heart surgery (two physicians), and the aim of reducing repeated surgeries (two physicians) were other reasons expressed. The Main reasons why surgery was applied instead of the percutaneous procedure were: the patient does not meet the eligibility criteria to undergo percutaneous intervention (four physicians); the longer follow-up of the traditional technique compared to the percutaneous one (one physician); PPV is still not actually as widely applied as the traditional procedure, making it necessary to assign the patient to a centre where the percutaneous procedure is more generally adopted (one physician).

Results of rating (mean, minimum and maximum rates) the treatment characteristics presented to the participants are summarized in Figure 1. Every characteristic was on average scored at least 5, which corresponds to the characteristic being considered to be of moderate importance. However, some characteristics were, on average, rated as more important than others and, while physicians and patients/caregivers agreed on the level of importance assigned to some of these attributes, different opinions emerged regarding some other characteristics. In fact, by ranking the characteristics according to the mean rate found in each subgroup of participants, it appeared that the risk of complications attributable to intervention delay is considered the most important, and the type and dimension of the scar the least important characteristic by both the physicians and patients/caregivers. However, while another most important characteristic for the patients/caregivers was the risk of complication during the months after the intervention (score=10), this aspect was ranked only the fifth most important aspect for physicians (mean score=6.9), and considered by them as less important than the risk of complications attributable to intervention delay (mean score=8.7), patient's fear for the next intervention (mean score=8.1), major procedural complications (mean score=7.9), and time necessary to return to everyday activities (mean score=7.7). The time elapsing until the successive intervention is considered necessary was ranked the seventh and the ninth most important characteristic for the patients/caregivers and for the physicians, respectively. Procedural costs appeared to be more important than the position and dimension of the scar, and the physicians appeared to consider this aspect as more important than the length and type of hospital stay or the length and time elapsing until the next intervention.

DISCUSSION

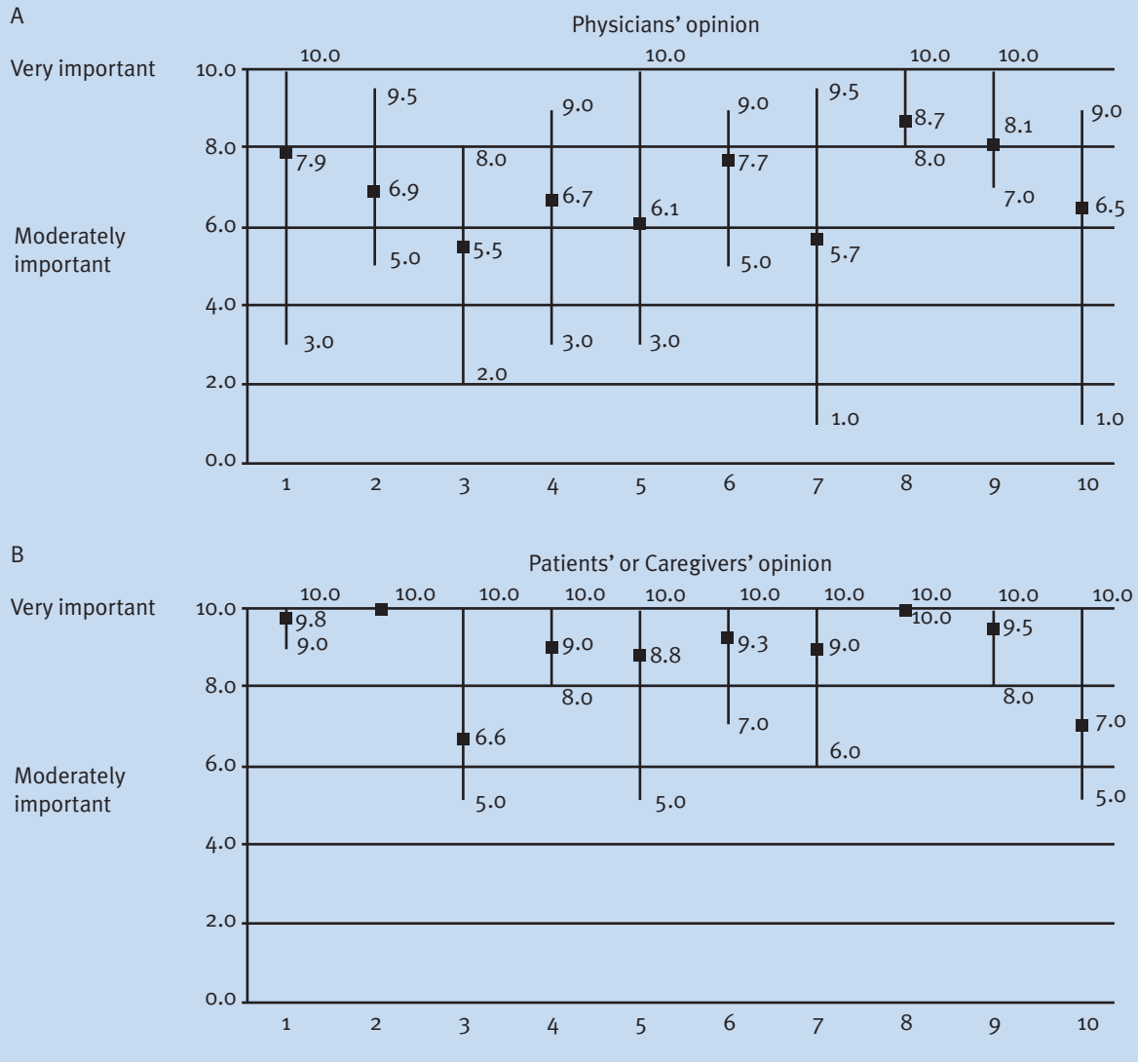
Current literature shows that, on the basis of clinical experience reported by experts, a number of issues are currently debated regarding the management of patients with RVOT dysfunction. In particular, 10 distinct aspects were identified as potentially relevant in the decision making process for selecting which treatment strategy to apply. These characteristics have different possible implications: some are more related to clinical issues (such as the risk of major procedural complications and the risk of complications occurring during the months after the intervention) while some are more related to patients' perception, (such as having pain after the intervention and being scared of the next intervention). Other aspects are more related to practical issues, like the dimension and position of the scar, while others focus on economic implications: e.g., the procedural costs, but also the type and length of hospital stay as well as long recovery times and related productivity loss. Regarding the time elapsing until the next intervention, whilst delaying it could compromise patients' clinical condition, intervening early is expected to negatively influence patients' quality of life and, in the long run, also their eligibility for further interventions that could be necessary.

On average, the survey showed that the importance of characteristics varies, and that they all could have a role in the process of decision making related to the management of target patients. However, results suggest that different levels of relative importance between the two subgroups of participants exist: while physicians and patients/caregivers seem to agree about the most important the least important aspects, they disagree with regards to other characteristics, e.g., risk of complications occurring during the months after the intervention for early degeneration, and the length of time elapsing until the next intervention is deemed necessary, which were assigned a relative lower importance by physicians than by the patients/caregivers.

Some limitations could be evidenced in this study. A small number of subjects participated in the survey (five physicians, two patients and two caregivers), which may affect the reliability of our results. Furthermore, the method used

FIG. 1

RESULTS OF RATING TREATMENT CHARACTERISTICS ACCORDING TO IMPORTANCE: COMPARISON BETWEEN PHYSICIANS (A) AND PATIENTS OR CAREGIVERS (B)



Legends

In X axis each number corresponds to the characteristics presented for rating: 1=risk of major procedural complications, which can lead to repeat the intervention, even in emergency rescue surgery, or to death; 2=risk of complications occurring during the months after the intervention requiring medical care, hospitalization or even to repeat the intervention; 3=dimension and position of the scar; 4=perception of pain after the intervention; 5=length of hospital stay and its type (for instance at intensive care unit) to perform the intervention; 6=time necessary to come back to do normal activities of daily life, like going to work (also for the parent taking care of the patient) or to school, doing leisure activities, sport, staying with friends and other people; 7=length of time (years) elapsing until the intervention has to be repeated; 8=risk of complications that can be due to intervention delay, like heart failure, arrhythmia, or sudden death; 9=perception of fear for the next intervention; 10=cost to perform the intervention: tests and examinations, instruments and equipment, anaesthesia, drugs, procedure/operative time, cost of intensive care, cost of hospital stay. Y axis shows the possible rates to be assigned to the characteristics. Results are shown as means (■) and minimum and maximum levels (light grey vertical lines).

in the survey, in which the participants were required to rate each characteristic but not to compare each other, can be considered as a non-optimal way to estimate the relative importance assigned to each characteristic; in other words, to estimate their willingness to give up some benefits of one treatment characteristic in order to gain benefits obtained from choosing a different option (e.g., reducing the risk of severe complications attributable to excessive intervention delay in exchange for having a long and painful recovery time). This study, which

to our best knowledge is the first attempt at investigating physicians' and patients' opinions towards different characteristics of treatments available to subjects with RVOT dysfunction, can be considered as a preliminary investigation in this field. However, our results encourage the conduction of more extensive research, with the specific aim of quantifying and comparing the relative importance assigned to each treatment characteristic relevant for each category of subjects interviewed, or any stakeholders who make, or could influence, decisions, and monitor the outcomes and/or costs of these decisions.

The management of patients with RVOT dysfunction requires a lifetime strategy, with close cooperation between cardiologists, pediatric cardiologists, surgeons and interventional cardiologists. Treating these patients should be considered as a long term investment which requires the identification of the best strategy to adopt, considering both present and future benefits together with present and future costs (or benefits forgone) derived from each possible option. Regarding costs, not only must present procedural costs be considered, but also other items, like direct costs (i.e., health care costs necessary to manage clinical failure of repeated procedures), indirect costs, (i.e., productivity loss by patients' and caregivers'), and intangible costs (i.e., impairment of patients' wellbeing). All these issues are actually relevant and must be taken into account for a complete estimate of the burden of illness experienced by patients with RVOT dysfunction, and to estimate the net benefit (value) deriving from the decisions made and procedures undertaken throughout the lifetime management of these patients.

Relevant research and investments have been conducted in recent years, with the objective of obtaining and implementing treatments which allow the improvement of the overall health benefits of patients. When the PPV procedure was introduced in clinical practice, decisions had to be based on the hope and expectation that this new procedure could be used as a bridge to delay surgery, when applicable, without compromising the ventricular function. It happened, in fact, that although there was no certainty about that, the experienced negative issues attributable to the need for repeated surgery over a patients' life-time were considered to be a good reason to try to delay surgery by performing PPV in a number of patients. As a result, more than 1000 patients in Europe have received the percutaneous intervention and some experience has been gathered on the real performance of this procedure. The most recent findings reported in the literature show promising results about the benefits attributable to the percutaneous procedure as a complementary option to surgery. However, any conclusion in this regard is still hard to reach: clinicians underline that the available knowledge and experience is still not sufficient to be sure about the best treatment/procedure option to choose. Furthermore, the process of decision-making actually involves a complex interaction between a number of aspects, which can have different relative importance according to the different subjects involved in the process. Additionally, all subjects carry their own set of needs, expectations and preferences, which are differently influenced by the point of view and role that they play in the healthcare system. Knowledge and awareness of patients' clinical needs, of the advantages and disadvantages of the available treatment procedures, as well as of opinions and preferences of the different subjects involved, can increase the chance of successfully applying the best treatment strategies, and all these characteristics should be considered as guides to decisions that have to be made and that are aimed at improving outcomes by efficiently allocating resources.

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