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Perioperative temperature is no predictor of pulmonary valve allograft function or the development of anti-HLA antibodies after the Ross procedure in adults

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Abstract

Objectives: Perioperative temperature has been suggested to be a marker of an immune reaction against allograft valves. We explored whether there is an association between perioperative temperature and pulmonary allograft valve function or the development of anti-HLA antibodies.

Methods: The highest temperature on each of the first five postoperative days was extracted from the records of 211 patients (79% male, mean age 45 ± 14 years) who had had a Ross operation. For further analysis, the area under the temperature curve of each patient was calculated and then tested for correlations with valve function. Two echocardiographic measurements, which were approximately 5 years apart from each other, were analyzed. In a subgroup of 160 and 100 patients, respectively, anti-HLA class I and II antibodies were measured and also tested for an association with perioperative temperature.

Results: After a median of 0.9 years, we observed a weak, but statistically significant correlation between perioperative temperature and the transvalvular pressure gradients (r=0.20, p=0.005). However, there was no such association after a median of 6.1 years, and there was no association with the grade of regurgitation at any time. The development of anti-HLA antibodies also appears not to correlate with perioperative temperature.

Conclusions: This study suggests that there is no important association between the temperature recorded during the first few postoperative days and the function or fate of pulmonary allograft valves or the development of anti-HLA antibodies.

Key words: immunology, rejection, surgery, transplantation, valves

Introduction

Deterioration of valve function after implantation of a cryopreserved valvular allograft can be frequently observed. A variety of risk factors have been identified, but the mechanisms promoting deterioration are poorly understood. Rejection of the allograft valve has been proposed as one possible mechanism, but has not been conclusively demonstrated in humans.

Postoperative fever has been implicated as a possible sign of rejection by some authors [1,2]. We have reported that the perioperative temperature was lower in patients who received a decellularized pulmonary allograft valve for reconstruction of the right ventricular outflow tract [RVOT] during repair

of congenital lesions or during the Ross operation [3]. Using the same methodology, we also observed a weak, but statistically significant association between perioperative temperature and the pressure gradients across the allograft valve, see figure 1. That observation was communicated as an abstract [4] and orally during meetings, but never published because we were sceptical about its validity. We iniated a follow-up study the results of which are reported herein.

Methods

At our department, the Ross-procedure is widely used in adults with aortic valve disease. Postoperatively, the patients are seen in regular intervals for clinical and echocardiographic follow-up. Details on the operative procedure and the clinical and echocardiographic results have been extensively published [5,6]. The study was approved by the local ethics committee and performed according to institutional guidelines. All patients gave informed consent.

One of these regular follow-up visits forms the basis for this report. A random sample of 211 patients had an transthoracic echocardiographic examination. Due to the cross-sectional design, the follow-up period was varying widely (median = 0.9 years postoperatively; minimum-maximum: 0.1-9.6 years). The clinical characteristics of the patients were extracted from the medical records and are given in table 1.

Measurement of perioperative temperature

In our clinic, rectal temperature is measured continuously during the stay on the intensive care unit (usually the first 24 hours postoperatively), and recorded once per hour. Thereafter, the rectal temperature is measured 3 times per day. The highest temperature on each day was extracted from the records. The course of the perioperative temperature is depicted in figure 2, as well as the method for calculating the area under the temperature curve [AUTC]. The AUTC as well as the highest and the lowest postoperative temperature were used as independent variables during the further analyses.

Table 1: Demographics of the patients studied

Variable	
male/female patients [n]	167 (79%)/ 44 (21%)
age, patients [years]	45 ± 14
duration of ECC [min]	213 ± 32
duration of x-clamp [min]	168 ± 27
allogeneic transfusions [n]	59 (28%)
diameter of allograft valve [mm] *	25.5 ± 1.5
age, donor [years] #	47 ± 10
AB0-mismatch [n] †	78 (71%)
sex-mismatch [n] ‡	58 (34%)

*: information not available in 9 patients
#: information not available in 57 patients
†: information not available in 101 patients
‡: information not available in 41 patients

Measurement of HLA antibodies

In a subgroup of patients during that first visit, blood was drawn for determination of panel reactive antibodies [PRA] (a measure of antibodies against class I human leucocyte antigens [HLA]) and anti-class II HLA antibodies [HLA2AB]. PRA were measured in 160 patients and HLA2AB in 100 patients. Whole blood was centrifuged immediately, and serum samples stored at -80°C until analysis. Detailed results on the measurement of anti-HLA antibodies, their frequency and their relation with allograft valve function are published elsewhere [7].

Echocardiographic follow-up

For further analysis, the results of a second echocardiographic follow-up visit (median = 6.1 years postoperatively; minimum-maximum: 1.8-14.6 years) in the same group was tested for associations with the perioperative temperature.

Echocardiography

For echocardiography, a Sonos 5 500 ultrasound system with a 2.5 MHz ultrasound transducer [Agilent Technologies, Andover, Ms] was used. Flow characteristics across the RVOT were measured by continuous wave [cw] Doppler from the left parasternal short axis view. Peak and mean transvalvular pressure gradients were determined by use of the modified Bernoulli equation ($\Delta p=4v^2$, where Δp is the pressure gradient, and v is the maximal flow across the valve). Color flow Doppler was used to detect pulmonary regurgitation. The severity was semiquantitatively assessed on the basis of the length and width of the regurgitation jet and the distance it reaches into the RVOT and graded into none, trivial, mild, moderate, moderately severe, or severe.

Statistical analyses

Categorial data are given as total numbers and relative frequencies. Continuous data are presented as mean ± standard deviation, except where otherwise stated. Echocardiographic measurements were compared using the Wilcoxon signed ranks test. Bivariate Pearson's correlation was used for testing for an association between perioperative temperature and the pressure gradients across the allograft valve. The Mann-Whitney U-test and the Kruskal Wallis test were used for testing for an association between perioperative temperature and reoperations and grade of regurgitation across the allograft valve, respectively. Multiple comparisons were corrected for using Bonferoni's method. A p-value < 0.05 was considered to indicate statistical significance. All analyses were performed using SPSS for Windows [release 9.0; SPSS; Chicago, Il].

Results

The results of the echocardiographic examinations are presented in table 2. There was a slight deterioration of allograft valve function over time.

Perioperative temperature and pressure gradients across the allograft valve

As already shown in figure 1, we observed a weak, but statistically significant association between the AUTC and the maximal pressure gradient across the allograft valve. A similar observation was made with regard to the mean pressure gradient (r=0.20, p=0.005).

However, at the time of the second echocardiographic examination, no such association was found for either the maximal pressure gradient (figure 3) or the mean pressure gradient (r=-0.02, p=0.80) or for the changes of maximal or mean trans-valvular gradient over time. In addition, neither the

Table 2: Pulmonary allograft valve function

Variable			**p**
follow-up [years] median minimum-maximum	0.9 0.1-9.6	6.1 1.8-14.6	
maximal pressure gradient [mmHg]	11 ± 8	15 ± 8	<0.001
mean pressure gradient [mmHg]	6 ± 4	8 ± 6	<0.001
transvalvular regurgitation [n] - none - trivial - mild - moderate - moderately severe - severe	 110 (58%) 36 (19%) 40 (21%) 3 (2%) 0 0	 101 (50%) 60 (30%) 33 (16%) 9 (4%) 0 0	0.07

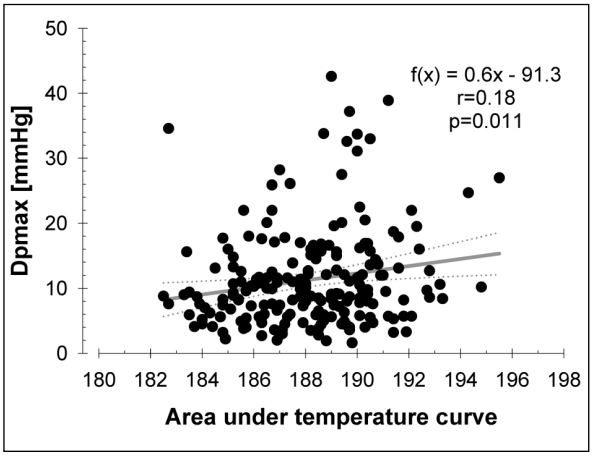

Figure 1: Scatterplot of the area under the perioperative temperature curve and the maximal pressure gradient across the allograft valve, first examination (0.9 years postoperatively).
A weak, but significant correlation between the variables was observed that can be expressed as a positive linear association. Shown as a bold dark line is the regression line, with their 95% confidence boundaries marked as dotted gray lines.

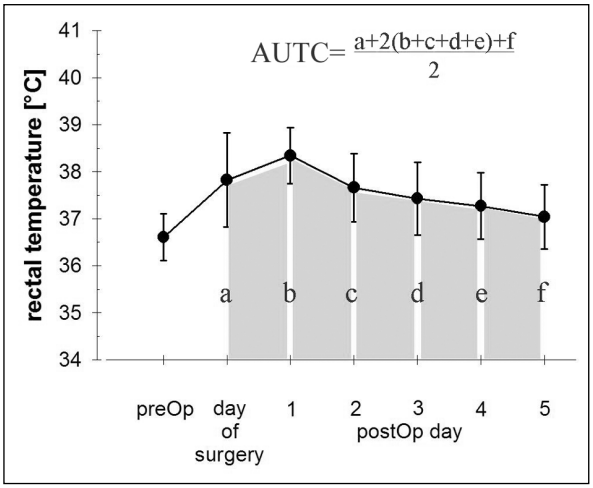

Figure 2: Measurement of perioperative temperature
The figure shows the mean rectal temperature (± standard deviation) of the patients. A significant change of the temperature with time is evident (p<0.001). The area under the temperature curve [AUTC] is calculated as shown for the first five postoperative days. Many patients did not stay longer in hospital, therefore, the analysis needed to be restricted to this period.

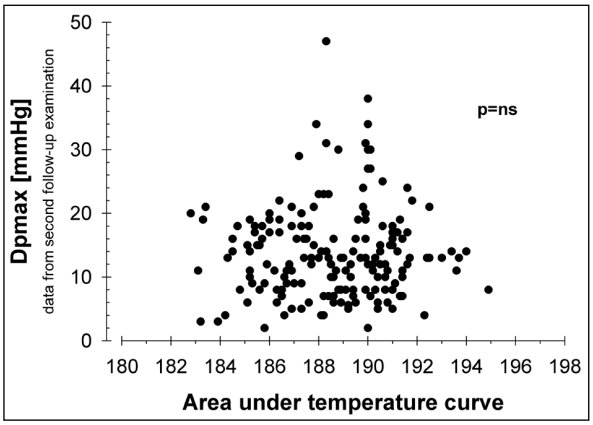

Figure 3: Scatterplot of the area under the perioperative temperature curve and the maximal pressure gradient across the allograft valve, second examination (6.1 years postoperatively)
No association between the variables is apparent (r=0.09, p=0.22).

highest or lowest recorded temperature showed any identifiable association with the pressure gradients or their change over time.

Perioperative temperature and regurgitation across the allograft valve

We did not observe a significant associaton between perioperative temperature and the grade of regurgitation across the allograft valve at any of the follow-up visits.

Perioperative temperature and reoperations

Overall, 5 patients (2.4%) were reoperated on the pulmonary allograft a median of 7.0 years postoperatively (minimum-maximum, 1.3-12.9 years). Neither the AUTC (p=0.17) nor the highest (p=0.16) or lowest (p=0.27) recorded temperature did differ between patients with or without reoperations.

Perioperative temperature and HLA antibodies

Among the subgroup of patients examined for anti-HLA antibodies, n=72 (45%) were positive for PRA and n=51 (51%) were positive for HLA2AB. Neither the AUTC nor the highest or lowest recorded temperature showed any associaton with PRA positivity. The AUTC tended to be lower in patients who were positive for HLA2AB, but that difference was very small (188 ± 2 vs 189 ± 2; p=0.04). No association was found between HLA2AB and the highest or lowest recorded temperature.

Discussion

In this study we demonstrate that perioperative rectal temperature cannot serve as a predictor for pulmonary allograft valve function at mid-term follow-up (a median of 6.1 years postoperatively). In line with other studies, we observed a slight deterioration of allograft valve function during the period under study. The mechanisms that promote this deterioration are controversely discussed, and an immune reaction against the allograft appears to be one of the most plausible explanations.

Implantation of a cryopreserved valvular allograft essentially is a transplantation of viable and non-viable tissue [8]. An immune reaction specifically directed against HLA determinants of the valve donor has been demonstrated by many groups, but neither measurements of anti-HLA antibodies nor HLA mismatch studies so far were able to conclusively prove the presence of rejection [2,7,9-14].

Implantation of a cryopreserved valvular allograft may – probably in addition to a specific immune response – also cause a foreign-body reaction [15]. Whatever the exact mechanism, it appears plausible that an immune reaction might in some way be operative in the deterioration of allograft valve function over time that is frequently observed [15-18]. The identification of a variable that predicts the fate of the implanted valvular allograft early on would offer the chance to try to suppress such an immune reaction and thereby probably preserve valve function.

Postoperative temperature has been suggested as a marker for rejection by some authors [1,2] and us [3]. Shapira et al. [1] reported a high frequency of unexplained fever in recipients of aortic allograft valves und suggested that this is a sign of low-grade rejection. Dignan et al. [2] found that patients with 2 mismatches on the HLA-DR locus significantly more often suffered postoperative fever. However, they did not observe an association between postoperative fever and structural degeneration of the implanted aortic allograft valves. In this study, we were unable to detect any relation between the presence of anti-HLA antibodies and perioperative temperature. In an earlier study, we reported that 24 patients who received decellularized pulmonary allograft valves had lower perioperative temperatures as compared to recipients of conventional allograft valves [3]. However, in an extension to that study, we observed no difference between recipients of decellularized and conventional allograft valves with regard to valve function or reoperations [18]. Therefore, any difference in perioperative temperature does not appear to be of any functional importance – an interpretion that is also supported by the findings reported herein and a study of Troost et al. [19]. In that study, no association between perioperative temperature (as expressed by the number of days with temperature > 38°C) and failure of RVOT allografts in patients with tetralogy of Fallot was found.

Our current study has several limitations. Besides its retrospective nature, the most important limitation appears to be the fact that only the first 5 postoperative days are covered. A detrimental immune reaction will probably become evident later and last longer than in these first few days. However, as shown, several studies before have explored whether perioperative temperature is of interest – ours being the largest one so far. Perioperative temperature might be expressed and analyzed in different variables: we have mainly used the area under the temperature curve as well as the highest temperatures recorded. Another consequence and limitation of the retrospective nature of the study is the fact that we were unable to distinguish fever due to infection from unexplained fever.

In summary, this study suggests that there is no important association between the temperature recorded during the first few postoperative days and the function or fate of pulmonary allograft valves or the development of anti-HLA antibodies.

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