Cardiology in the Young

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Immunological differences between heart- and kidney-transplanted children: a cross-sectional study†

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Abstract

Post-transplantation lymphoproliferative disorder is a potentially mortal complication after heart transplantation in children. As the immune system plays a crucial role in the development of lymphoma, we explored the influence of thymus function in relation to immunosuppressive treatment in organ-transplanted children and healthy control subjects. A prospective case–control study was performed at a single centre, in which 36 children who had undergone heart transplantation were compared to two control groups: 34 kidney-transplanted children and 33 healthy age- and sex-matched children. T- and B-lymphocyte subtypes and monocytes were analysed by flow cytometry, and T-cell receptor excision circles were assessed using quantitative polymerase chain reaction. Heart-transplanted children had a lymphocyte profile characterised by reduced or absent thymic function with low numbers of T-cell receptor excision circles and total and naïve T cells, together with immune activation against the allograft. Despite similar immunosuppressive treatment, the kidney-transplanted group showed an activated T-lymphocyte compartment.

The discovery of anti-thymocyte globulin with the ability to suppress the thymus-derived T cells was crucial for the advent of heart transplantation. The most devastating side effect of the immune suppression is post-transplant lymphoproliferative disorder.[1] The immune suppression is suggested to cause an imbalance between the protective T cells and the B cells, which contain the lymphoma-driving Epstein–Barr virus.[2]

We noted an increased incidence of post-transplant lymphoproliferative disorder among children who had undergone heart transplantation at our centre. An analysis revealed the following risk factors for post-transplant lymphoproliferative disorder: sternotomy during infancy; mismatch concerning Epstein–Barr virus infection; hypoplastic left ventricle; surgically palliated CHDs; number of surgical events; and immunosuppressive treatment with tacrolimus compared with cyclosporine.[3] The identified risk factors led us to suspect a more complex aetiology of post-transplant lymphoproliferative disorder than just immune suppression. Immunological abnormalities are linked to CHDs in some genetic syndromes, for example the 22q11.2 microdeletion syndrome (DiGeorge syndrome). There are also reports of a compromised immune system in a wider range of CHDs.[4,5] The thymus blocks access to the heart and must be removed totally or partially during paediatric cardiac surgery. Thymectomised individuals have been shown to have aberrant T-cell function.[6]

Kidney-transplanted children receive a similar immune suppression therapy as heart-transplanted children but have a lower risk of post-transplant lymphoproliferative disorder (1–2% versus 3–20%).[7–9]

To understand the immunological differences between heart-transplanted and kidney-transplanted patients, we investigated the immune system of heart-transplanted children, focusing on T-lymphocyte populations, which we compared with kidney-transplanted children and a healthy control group. Our hypothesis was that heart-transplanted children had an impaired thymus function.

Materials and methods

A prospective, cross-sectional case–control study was conducted in 2018, including all heart-transplanted children between 2004 and 2018 in Gothenburg, one of two Swedish centres performing paediatric cardiac surgery and all kidney-transplanted children at the same institution. Demographic data and data regarding the indication for transplantation, CHD, immunosuppressive therapy, and transplant rejection were gathered from the medical records. A healthy

Table 1. Baseline demographics of the subjects and duration of immune suppression

	HTX (n = 36)	KTX (n = 34)	Healthy (n = 33)	p-value HTX versus KTX	p-value HTX versus healthy	p-value KTX versus healthy
Age, years, median (range)	13.6 (1.8–22.1)	12.8 (3.3–16.7)	13.0 (2.5–24.0)	0.16	0.53	0.92
Gender, female/male, n	15/21	11/23	11/22	0.46	0.62	1.00
Caucasian ethnicity, n Ratio of Caucasians to non-Caucasians	33/3	31/3	33/0	1.00	0.24	0.24
Transplant indication	CHD 20/36 CMP 16/36	CM 31/34				
Duration of immunosuppressive treatment, years (median, range)	5.1 (0.1–12.4)	6.1 (0.2–15.0)	–	0.96	–	–

HTX, heart-transplanted subjects; KTX, kidney-transplanted subjects; Healthy, healthy controls; CMP, cardiomyopathy; CM, congenital malformation.

age- and sex-matched control group was recruited. Subjects with any comorbidity, including immune dysfunction, were excluded.

Fresh, whole blood was used to determine the absolute numbers and proportions of T and B lymphocytes, natural killer cells, myeloid cells, and subpopulations thereof as proposed by the Human Immunophenotyping Consortium with minor modifications.[10] To determine the number of T-cell receptor excision circles, DNA was extracted from samples of fresh, whole blood using the QIAamp Blood Mini Kit (Qiagen, Venlo, the Netherlands), followed by a triplex real-time quantitative polymerase chain reaction for T-cell receptor excision circles and endogenous reference gene glyceraldehyde-3-phosphate dehydrogenase.[11] Detailed description of the methods is provided as supplementary information. Table S1 shows the characteristics of the different immune cell types.

Statistical methods

Demographic and immunological variables were compared using the Mann–Whitney U-test and Fisher's exact test when appropriate. The p-values were adjusted for multiple testing using the Benjamini–Hochberg procedure. The proportions of cellular and humoral rejections among the heart-transplanted and kidney-transplanted patients were compared using the chi-square test. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using the R ver. 4.0.2 software.

Results

A total of 103 subjects were recruited, and the baseline data for the three groups are presented in Table 1. There were no differences regarding age, gender, or ethnicity between the three groups. The durations of immunosuppressive treatment, that is time between transplantation and collection of blood sample, were similar between the groups: 0.1–12.4 (median 5.1) years for heart-transplanted children and 0.2–15.0 (median 6.1) years for kidney-transplanted children.

The indications for transplantation in the heart-transplanted group were CHD (n = 20) and cardiomyopathy (n = 16). Partial or total thymectomy was performed in 19 subjects (17 in infancy) with CHDs and in four (infancy) with cardiomyopathy. The indications for transplantation in the kidney-transplanted group were congenital malformation or condition (n = 31); kidney failure due to medication (n = 1); kidney failure secondary to a severe infection (n = 1); and kidney failure with unclear aetiology (n = 1). Age at transplantation for the heart-transplanted group was 3 weeks to 17 (median 6) years and for the kidney-transplanted group 1 to 16 (median 6) years. There was no case of re-transplantation.

Table S2 summarises the transplantation-related medications. The induction treatment was more aggressive in the heart-transplanted group, while the doses of steroids were higher among the kidney-transplanted patients. The target level of tacrolimus was initially higher among the heart-transplanted patients, after 12 months it was similar. The immunosuppressive treatment at the time when blood samples were obtained differed slightly, target levels for tacrolimus were rather similar, while mycophenolic acid was more frequently used in the kidney-transplanted group, and certican was used in the heart-transplanted group but not in the kidney-transplanted group. Steroids were only used in the kidney-transplanted group (31/34 patients).

Regarding rejections, there was not any statistical difference between the kidney-transplanted and heart-transplanted groups (p = 0.085). For details, see Table S3.

Five subjects in the heart-transplanted group had received treatment for post-transplant lymphoproliferative disorder; all were born with CHDs with a dominating right ventricle and thymectomised before 1 year of age.

Since the functional impact of absolute versus relative numbers of lymphocyte subsets is not clear, we present both absolute and relative numbers for all lymphocyte subsets in Table S4 and Table S5, respectively. We however focused the analyses on absolute numbers in the major lymphocyte populations and relative numbers in the smaller subpopulations.

The heart-transplanted group had markedly lower numbers of T-cell receptor excision circles and recent thymic emigrants than both the kidney-transplanted healthy control groups, confirming the impaired thymic function in the heart-transplanted group (Table S4, Fig 1a and b). The heart-transplanted group also had lower absolute numbers of mononuclear cells, lymphocytes, total T lymphocytes, helper T cells, naïve helper T cells, and naïve cytotoxic T cells than in either the kidney-transplanted or healthy control group (Table S4, Fig 1a and b). The differences were generally larger when compared with the kidney-transplanted group, reflecting higher levels of T cells in the kidney-transplanted group than in the healthy control group. The same accounts for cytotoxic T cells and B cells, with high numbers in the kidney-transplanted group. Considering the T-cell subpopulations, the heart-transplanted group had lower frequencies of naïve helper T cells, recent thymic emigrants, and naïve T regulatory cells than in either the kidney-transplanted or healthy control group (Table S5, Fig 2a and b).

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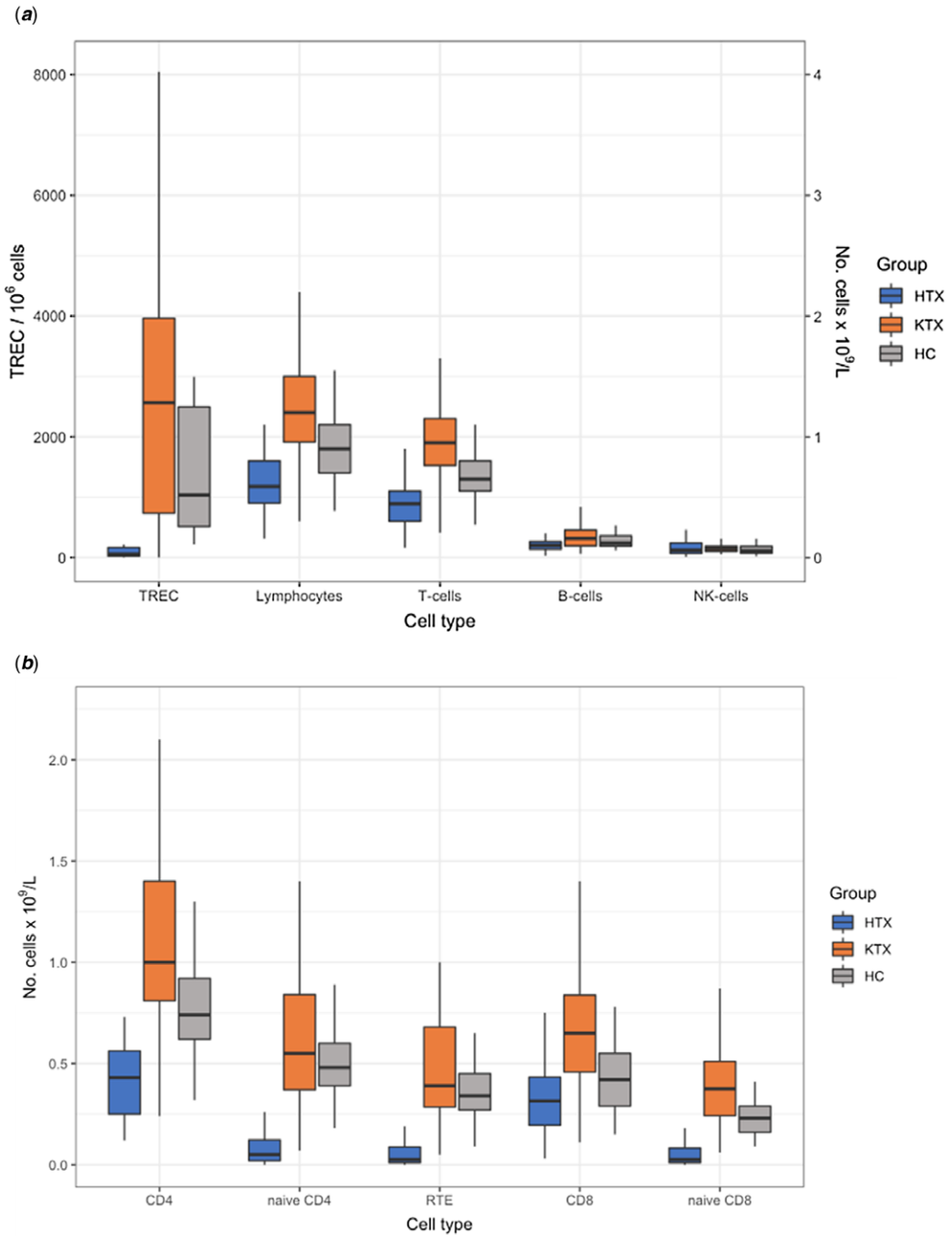

Figure 1. T-cell receptor excision circles (TREC) and subpopulations of lymphocytes in blood.

In contrast, the frequencies of antigen-experienced helper T cells and cytotoxic T cells, for example effector memory helper T cells and cytotoxic T cells, were higher in the heart-transplanted group than in either the kidney-transplanted or healthy control group. Among the helper T-cell subsets, the relative numbers of T cells type 1, helper T cells type 17, and follicular helper T cells were higher in the heart-transplanted group than in either the kidney-transplanted or healthy control group.

When turning to the kidney-transplanted group, the absolute numbers of mononuclear cells, lymphocytes, total T cells, helper T cells, cytotoxic T, and naïve cytotoxic T cells were higher, as compared with either the heart-transplanted or healthy control group (Table S4, Fig 1a and b). The absolute numbers of naïve helper T cells, recent thymic emigrants, and B cells were higher in the kidney-transplanted group than in the heart-transplanted group but were like those in the healthy control group. The relative numbers of naïve helper T cells, recent thymic emigrants, and naïve T regulatory cells in the kidney-transplanted group were lower than in the healthy control group (Table S5, Fig 2a and b). In contrast, the central memory helper T cells showed the opposite pattern, in which the relative numbers in the kidney-transplanted group were lower than in the heart-transplanted group, but higher than in the healthy control group. Several antigen-experienced helper T cells and cytotoxic T-cell populations that are central to memory and effector memory helper T cells and cytotoxic T were present in lower numbers in the kidney-transplanted group than in the heart-transplanted group but in similar numbers in the healthy control group. The helper T-cell cell subsets appeared at similar relative numbers in

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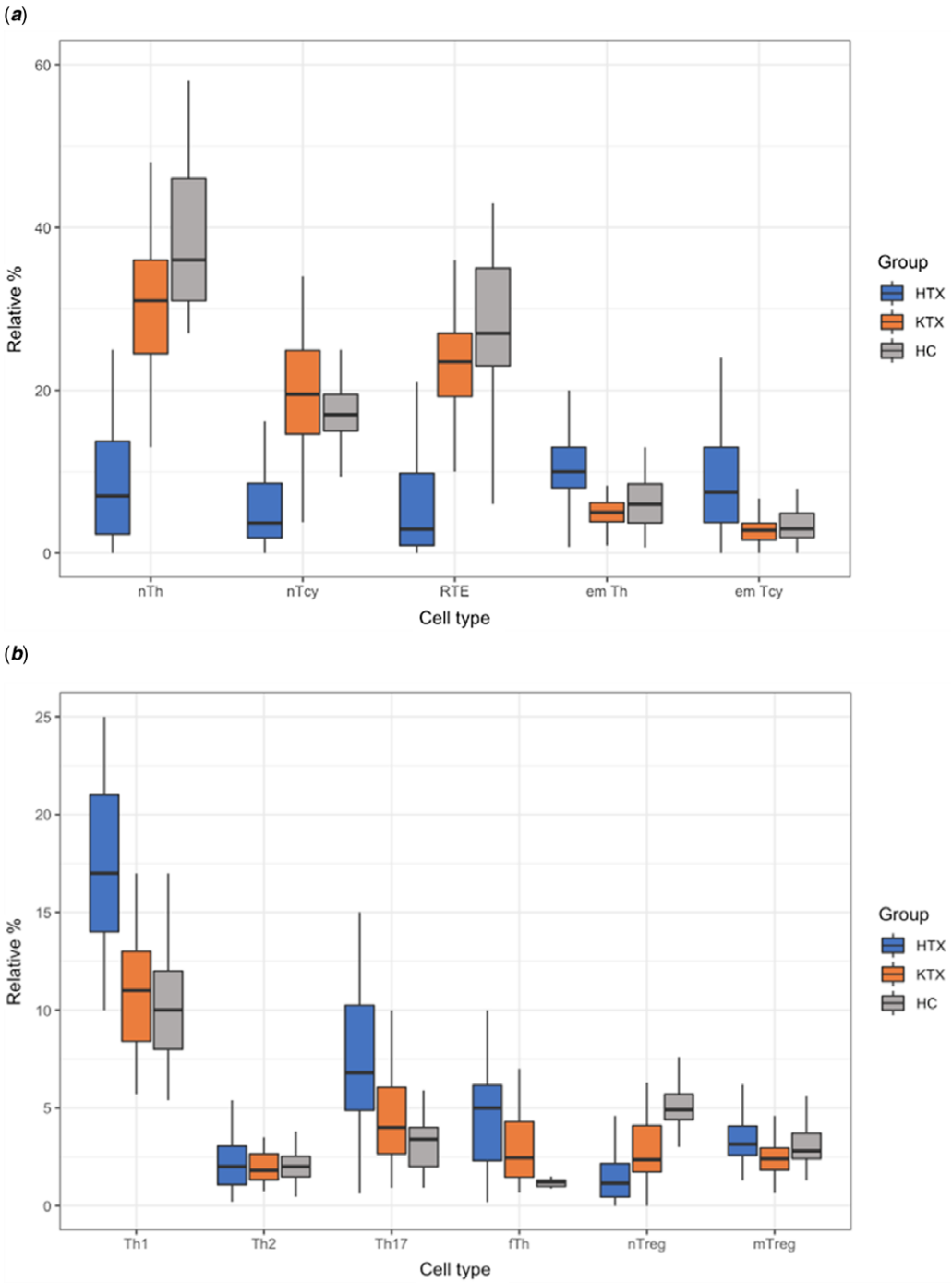

Figure 2. Subpopulations of lymphocytes in blood.

the kidney-transplanted and healthy control groups, whereas the helper T cells type 1 and helper T cells type 17 cell numbers were lower in the kidney-transplanted than in the heart-transplanted group.

Discussion

The most striking finding of the present study is that heart transplantation is associated with low thymic output and low numbers of the major T-cell populations. In contrast, the kidney-transplanted group is characterised by high absolute numbers of cells of the major T-cell populations, with an activated profile.

During corrective heart surgery or during surgery associated with heart transplantation, removal of thymus is often necessary, especially in extensive surgery performed early in life. The risks associated with thymectomy are currently presumed to be minor compared to the benefits of this complicated surgery. Several studies have confirmed a long-term impact on the numbers and functions of T cells after thymectomy.[6,12,13] There are also reports of recovery of the thymus after thymectomy.[14]

The thymus is closely related to the heart during embryogenesis, where parts of the heart as well as the thymus originate from the neural crest. Malformations and syndromes that include defects in both the heart and the thymus have been described for decades, where thymus aplasia is at one end of the spectrum.[15]

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There are descriptions of CHDs and cardiomyopathy associated with primary immune deficiencies, for example atrial septal defects in patients with serine threonine kinase 4 deficiency and cardiomyopathy in patients with Barth syndrome.[16] Recently, impaired numbers of T receptor excision circles have been documented in newborns with CHD with and without known immune disorders.[4] In the post-heart transplant scenario, the thymus potentially has a pre-existing weakness associated with the heart disease and in addition been subject to one or several surgical traumas.

Immunosuppression in heart transplantation and kidney transplantation

In our cohort, there were some differences between the groups in the strategies for transplant-associated medication (Table S2). For example, during 2007–2015, anti-thymocyte globulin was administered at the time of transplantation to the heart-transplanted group, whereas no induction therapy was administered to the kidney-transplanted group. The effects of anti-thymocyte globulin and steroids are however time-limited.[17–20] The target level of tacrolimus is higher immediately after heart transplantation but reaches the same level as after kidney transplantation at 1-year post-transplantation. In addition, only minor reductions in the T-cell subsets during treatment with tacrolimus and/or mycophenolate mofetil have been previously shown.[21–23] These differences cannot explain the differences in immune function presented in our study as the T-cell response was totally opposed between the two groups.

Reduced thymic function in the heart-transplanted group versus activated immune function in the kidney-transplanted group

The low T receptor excision circle counts in combination with low numbers of naïve T cells and recent thymic emigrants are confirmation of impaired thymic function in the heart-transplanted group. The pattern is like that reported after thymectomy not associated with heart transplantation.[6] This supports our hypothesis that thymectomy, rather than immunosuppression or other transplant-related factors, is the main reason for the low T-cell counts.

While the absolute numbers of helper T cells and cytotoxic T cells are low in the heart-transplanted group, with the most pronounced differences observed for the naïve populations, most of the memory populations do not differ from those in the healthy control or kidney-transplanted group. In analogy with what has been reported after thymectomy, we interpret this as primarily an effect of homeostatic proliferation of memory T cells.

The relative numbers of naïve T cells in the heart-transplanted group are lower than in the healthy control or kidney-transplanted group, whereas the antigen-experienced populations in the heart-transplanted group are expanded, which probably reflects a combination of homeostatic proliferation and immune activation. The immune activation is affecting the T helper cells subsets, with an increase in helper T cells type1 and helper T cells type 17 cells and low numbers of Treg cells. Despite the low absolute numbers of T cells, the relative number of class-switched memory B cells is not different in heart transplantation, which suggests that the effect on the T-cell compartment is not impairing the T-cell-dependent activation of B cells. We do not have an explanation for the difference in total B cells after heart transplantation, compared to kidney transplantation; it might be due to the differences in the activation of the immune system.

Thymic output, as assessed by the T receptor excision circles counts and absolute numbers of recent thymic emigrants and naïve T cells, does not seem to be affected after kidney transplant, as it is not different between the kidney-transplanted and healthy control groups (Table 1). The high absolute numbers of both helper T cell and cytotoxic T cells seen in the kidney-transplanted group is thereby not explained by an increased egress of naïve cells from the thymus. Instead, it may be due to activation and proliferation in the periphery because of chronic immune activation by the allotransplant. It is noteworthy that the high numbers of T cells occur in the presence of an effective immunosuppressive treatment and a low frequency of rejection.

The activation of the T-cell compartment also affects the relative numbers of T cells, with a predominance of antigen-experienced cells over naïve cells, together with a low frequency of T regulatory cells, giving a similar helper T-cell profile as in the kidney-transplanted and the heart-transplanted groups (Table S5).

The high absolute numbers of T cells in the kidney-transplanted group possibly reflect a constant immune stimulation in combination with normal thymic function. The immune profiles of the heart-transplanted and kidney-transplanted groups are similar, with signs of chronic immune activation by the allotransplant. The helper T cells type1, helper T cells type2, helper T cells type 17, and T regulatory ratios indicate an activated T-cell compartment that is trying to reject the transplant, even though the impaired thymic function is limiting the absolute numbers of T cells in the heart-transplanted group. Increased immunological activity is a natural response to allotransplantation, and immunosuppressive therapy is administered to control this response in order to accept the transplanted tissue. Therefore, the differences between the heart-transplanted and the kidney-transplanted groups were unexpected, especially the low absolute numbers of T cells in the heart-transplanted versus the high numbers of activated T cells in the kidney-transplanted group. However, a limitation of the study is that we did not investigate the degree of exhaustion among the T cells.[24,25] The differences in T-cell depletion strategies in the induction phase between the heart-transplanted and kidney-transplanted groups may have influenced the long-term rejection frequencies. The expected outcome from these differences would be a lower frequency of rejection in the heart-transplanted group.[26] However, this was not observed.

Implications of reduced thymus function following paediatric heart transplantation

There is growing body of knowledge as to how the immune system copes with viruses to prevent the development of malignancy.[27] It is generally accepted that a sufficient number and function of naïve T cells is necessary to fight new pathogens, for example Epstein–Barr virus infection of an immune-naïve individual.[28] After kidney transplantation, the 5-year incidence of post-transplant lymphoproliferative disorder is about 1%, as compared to 8% after heart transplantation.[7–9] This difference has been attributed to the higher doses of immunosuppressive drugs administered after heart transplantation, although early reports on post-transplant lymphoproliferative disorder suggested a more complex reason.[1] Our findings show profound differences in the immune function between heart- and kidney-transplanted children. The differences between our groups are related to the thymus, and our results indicate that the normal T-cell-mediated immune surveillance of Epstein–Barr virus is more impaired in heart-transplanted than in kidney-transplanted subjects.[29]

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The development of post-transplant lymphoproliferative disorder is complicated, and there is always a risk related to immunosuppressive therapy, which seems to be increased in thymectomised individuals.[3,30] Thymus transplantation is available at some centres and performed in subjects born with thymus aplasia.[31] The vulnerable group of children born with CHD requiring early and extensive surgery including total thymectomy would benefit if autologous transplantation of thymic tissue could be made possible for them.

In summary, the lymphocyte profiles of patients who had undergone heart transplantation are dominated by the effects of impaired thymic output, leading to low absolute numbers of T cells. In contrast, kidney-transplanted patients have high numbers of activated T cells, reflecting a state of chronic immune activation.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951122001743

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation in Sweden and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees in Gothenburg. The study was approved by the Central Ethical Review Board at the University of Gothenburg (Dnr. 243-17). Written informed consent was obtained from the participants and their caretakers.

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