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ÜRƏK VƏ BÖYRƏYİN EYNİ VAXTDA TRANSPLANTASİYASI: KLİNİK PRAKTİKADAN MƏLUMAT

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***Xülasə**. Məqalədə müəlliflərin eyni vaxtda ürək və böyrək transplantasiyası üzrə apardıqları operasiya haqqında məlumat verilmişdir. Bu, müəlliflərin Ukraynada multiorqan transplantasiyası üzrə ilk təcrübəsidir.*

Mitral qapaq stenozu ilə birgə sol mədəciyin arxa-yan divarına sirayət etdiyinə görə operativ müalicəyə tabe olmayan xronik böyrək xəstəliyinin terminal mərhələsi olan 51 yaşlı xəstəyə eyni vaxtda ürək və böyrək köçürülmüşdür. Xəstədə erkən posttravmatik dövr böyrək transplantatının funksiyasının kəskin çatışmazlığı ilə ağırlaşmışdır. Bu ağırlaşma hemodializ kursları vasitəsilə aradan qaldırılmışdır. Təqdim edilən klinik müşahidə ürəklə böyrəyin eyni vaxtda transplantasiya edilməsinin mümkünlüyünü, yaxın və uzağ nəticələrinin ümidverici olduğunu nümayiş etdirir.

***Açar sözlər**: ürək və böyrəyin eyni vaxtda transplantasiyası, multiorqan transplantasiyası, "ürək və böyrək" kompleksi*

***Ключевые слова:** одномоментная трансплантация сердца и почки, мультиорганная трансплантация, комплекс «сердце-почка»*

***Key words:** simultaneous heart and kidney transplantation, multiorgan transplantation, "heart-kidney" complex*

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CLINICAL OUTCOME OF SIMULTANEOUS HEART AND KIDNEY TRANSPLANTANT FROM A SINGLE DONOR

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The presented clinical case is the first experience of multi-organ transplantation in Ukraine. The surgery involved transplanting both a heart and a kidney into a 51-year-old patient with severe calcification of the mitral valve involving the posterior-lateral wall of the left ventricle, which is not amenable to surgical correction and end-stage chronic kidney disease, underwent orthotopic simultaneous heart and kidney transplantation. The early postoperative period was complicated by the development of acute renal failure of the transplant, which was corrected by courses of haemodialysis.

This clinical observation underscores the feasibility of simultaneous heart and kidney transplantation, offering promising short-term and long-term outcomes.

The demand for the "Heart-Kidney" transplantation complex has been steadily rising each year. Over a three-month period while awaiting transplantation, it has been observed that 21% of patients suffering from chronic renal failure (CRF) and requiring hemodialysis succumb to mortality, whereas the corresponding figure for patients with CRF who do not require hemodialysis is 7% [1,2].

Simultaneous heart and kidney transplantation is the gold standard in treatment of patients with heart failure and progressive chronic renal failure [3-5]. This procedure was first described in 1978 by Norman et al.,

and is still the only effective method of treating patients with combined critical cardiac and renal disorders [6].

Since the need for organs exceeds the actual number of donors, the decision to distribute two or more organs to one recipient requires a multidisciplinary team to discuss the risks and benefits of simultaneous transplantation with the careful subsequent selection of recipients to achieve the best post-surgery results [1].

According to the United Network for Organ Sharing (UNOS) data, 736 of "Heart-Kidney" complex were conducted for adults and 13 for kids in the United States of America (the USA) within the 2-year-period (2020-2021). 1-year survival of adult patients comprised 89.4%, of children – 75.2%.

As stated in the Eurotransplant registry, 13 simultaneous heart and kidney transplantation operations were performed in Europe during 2021-2022.

Even though the number of performed multi-organ transplants is increasing every year, there are still no generally agreed criteria for the selection and management of this category of patients [1, 7, 8].

The authors claim that selection criteria for combined heart and kidney transplantation are similar to those used to put patients on the waiting list for isolated heart transplantation and isolated kidney transplantation. Dilated cardiomyopathy (72%), ischaemic cardiomyopathy (15%) and congenital cardiac defects (7%) were identified as the most common cardiac diseases [3, 9-12].

In the open sources, we did not find any reports on successful simultaneous orthotopic heart and kidney transplantation in patients with calcific cardiac disease and end-stage chronic renal disease.

Our clinical case is unique because the development of the disease was atypical as compared to the cases described in the literature. In this case, the patient's chronic renal failure progressed for years, the patient had to undergo continuous haemodialysis courses. This led to the development of a sequential pathogenetic chain of metabolic and electrolyte disturbances, which led to the progression of calcifying cardiac disease with critical mitral valve damage with spread to the left ventricular wall and lesion of coronary arteries.

We present our own clinical supervision, which is the first case of multi-organ transplantation in Ukraine.

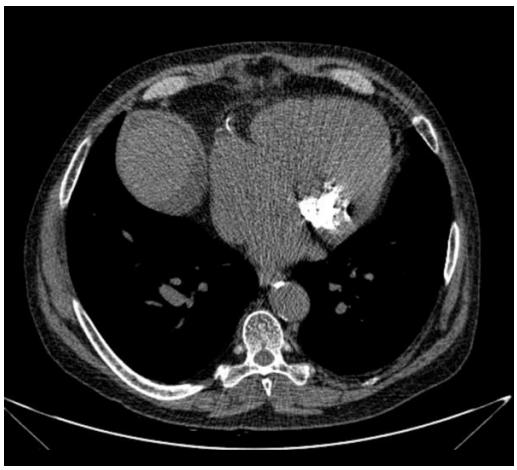
Patient P., 51 years old, urgently admitted to the Heart Institute State Institution of the Ministry of Health of Ukraine for a simultaneous orthotopic heart and kidney transplantation.

As we know from the medical history, the patient was diagnosed with chronic 5D degree renal disease, chronic glomerulonephritis in 2005. Since then, the patient has had to undergo regular sessions of renal replacement therapy under the supervision of a nephrologist at his place of residence. In 2019, due to deteriorated condition, a need for permanent haemodialysis occurred; the patient has been then included in the waiting list for a kidney transplant.

In 2020, due to the progression of the primary disease, the patient began to notice the symptoms in the form of breath shortness at rest, pain in the heart area and lower extremities swelling episodes. The patient has been admitted to the Heart Institute State Institution of the Ministry of Health of Ukraine for examination and decision on further treatment tactics.

The ECG revealed pronounced calcification of the mitral annulus with transition to the leaflets and spread to posterior-lateral wall of the left ventricle (LV). The back wall of the LV is hypertrophied (13 mm), the interventricular membrane is 15 mm. The global LV contractile function is preserved (LV ejection fraction – 62%). Hypertension in the small blood circulation was detected, the systolic pressure in the pulmonary artery reached 80 mm Hg.

Based on multispiral computed tomography of the chest cavity with intravenous contrast, caseous (mostly annular and spreading to the left ventricle myocardium wall) mitral annulus calcification and pronounced calcification of coronary arteries were detected (Figure 1, 2).



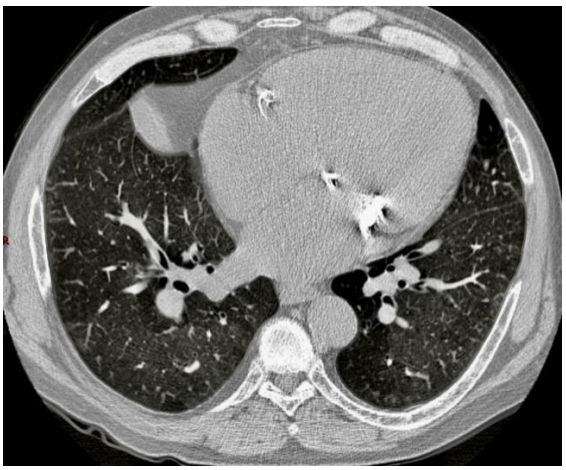


Fig. 1, 2. Multispiral computer tomography of the chest cavity: pronounced mitral annulus and coronary arteries calcification is detected

Based on coronary ventriculography (CVG), pronounced atherosclerosis of coronary arteries was detected: the trunk of the left coronary artery (LCA) – 40% stenosis, the anterior interventricular branch (LCA) – 55% stenosis in the proximal part, 30% stenosis – in the distal part, the diagonal branch of the 1st LCA – stenosis of 40% in the mouth, enveloping branch of the 1st LCA – stenosis of 40-50%. The trunk of the right coronary artery (RCA) – 40-50% stenosis, 40% stenosis of the middle third of the RCA, 30-40% stenosis – of the posterior interventricular and lateral branches of the RCA.

Diagnosis: Calcifying cardiac disease: 3rd degree combined mitral valve disease with stenosis predominant, 2nd degree moderate tricuspid valve insufficiency. IHD. Stenosing coronary sclerosis (according to CVG – multivessel lesioning of coronary arteries). 2nd degree hypertension in the pulmonary artery system. II B (II B) HF (Heart Failure) with preserved systolic function of the left ventricle (EF = 61%), functional class III according to NYHA. Chronic renal disease, stage 5-D: chronic glomerulonephritis (glomerular filtration rate (GFR) = 15 mL/min/1.73/m2). Scheduled dialysis since 2005. Secondary hyperparathyroidism.

The case conference involving cardiac surgeons, anaesthesiologists and cardiologists was conducted. Due to the impossibility of mitral valve prosthetics and coronary bypass surgery, it was decided to include the patient in the waiting list for a heart transplant. Given the need for multi-organ transplantation, the patient was assigned an I A status of emergency in the Unified state information system of transplantation (USIST) system.

The patient's condition proceeded deteriorating due to both the progression of the calcifying cardiac disease and increase in the number of haemodialysis sessions, thus the occurrence of the most compatible donor (matching all indicators) made it possible to perform the heart and kidney transplantation.

11/22/2021 – surgery: orthotopic simultaneous heart and kidney transplantation. Once the donor organs were delivered to the surgery room, the patient underwent a median sternotomy under general anaesthesia. The pericardium was dissected, and artificial circulatory system was gradually connected and started. Cardiectomy. Bicaval technique-based implantation of a donor heart.

Warming up to 37.5 C. Cardiac activity was restored. The artificial circulatory system was gradually stopped and disconnected. The main stage of surgical intervention was performed under conditions of superficial hypothermia (32 C). The total duration of artificial blood circulation equalled 200 minutes, the time of aorta compression – 52 minutes. Once sternotomy access was closed, the next stage has begun.

The common iliac and renal arteries were isolated and mobilized by a pararenal approach on the right, and they were taken in a retainer. An end-to-side anastomosis with renal and inferior vena cava was formed step

by step. An anastomosis was gradually formed between the renal artery and the common iliac artery. The right ureter was isolated, and was anastomosed with the own ureter of the donor kidney in a side-to-side manner. Haemostasis control. Drains are installed. The wound was sutured layer-by-layer.

Total duration of surgeries has made up to 6 hours and 50 minutes.

After the surgery, the patient was transferred to the Intensive Care Unit (ICU).

Post-surgical management was carried out according to established protocols, which included haemodynamic support (cardiac index > 2.5 L/min/m^2, central venous pressure < 10 mm Hg and pulmonary artery wedge pressure < 10 mm Hg), control of diuresis and early activation of the patient.

Post-surgery period in terms of cardiovascular system was uneventful. The duration of artificial lung ventilation has made 12 hours after the surgery. Inotropic support (dobutamine) was provided in the first 14 hours after surgery in minimal doses. Vasopressor support (norepinephrine) in the range of 50-150 ng/kg/min was performed during the first 38 hours. The operation of the donor heart was evaluated clinically and according to the data of the transthoracic echocardiographic examination – the cardiac function is satisfactory.

The course of early post-surgery period in terms of urinary system was complicated by the development of acute renal failure of the transplant. During the first 48 hours after surgery, diuresis was less than 150 mL/day. Despite optimal medical treatment, an increase in urea and creatinine levels, absence of urine, and worsening of the patient's general condition were determined. Renal replacement therapy sessions were started on the third post-surgery day. On the 5th day, excretory urography was performed, where positive dynamics of excretion of the contrast agent was noted. The normalization of lab parameters and daily increase in the amount of urine was determined. The patient underwent 4 courses of haemodialysis within 1 week (Table). The patient's condition remained satisfactory. On the 12th day of the patient's stay in the Intensive Care Unit, the patient was transferred for further treatment in the hospital.

Immunosuppressive and antiviral therapy was carried out according to the existing scheme: antithymocyte globulin, methylprednisolone, tacrolimus, mycophenolic acid/mycophenolate mofetil. The correction was carried out according to the level of concentration of tacrolimus in the blood.

Endomyocardial biopsies were performed on weekly basis during the first month and on monthly basis during the following 5 months. The degree of acute cellular rejection and antibody mediated rejection was determined based on the results of pathohistological and immunohistochemical examination of biopsies obtained during endomyocardial biopsy and classified according to the International Society for Heart and Lung Transplantation (ISHLT) classification.

On the 22nd post-surgery day, the patient was discharged from the hospital for rehabilitation under the supervision of a cardiologist and a nephrologist at the place of residence.

Tab. **Dynamics of the development of acute renal failure of the transplant in early post-surgery period**

	Before surgery	P/s day 1	P/s day 3	P/s day 6	P/s day 10
Creatinine (μmole/L)	190	220	360	135	93
Urea (mmole/L)	23.5	31	40.7	9.8	6.2
Albumin (g/L)	32	29	22.5	34	40.5
Daily diuresis (mL)	700	100	150	1200	1500
GFR (CKD-EPI) mL/min/1.73 m^2	32	28	16	51	80

After a year of supervision, the patient had no complaints. The patient underwent non-invasive examination methods: load tests with dosed physical activity (treadmill – test), trans-thoracic echocardiography, holter – ECG, which did not reveal abnormalities in the work of the heart. Based on the lab data and kidneys ultrasound, the function of the transplanted kidney is preserved. Correction of immune-suppressive medications was carried out according to the scheme. The follow-up is still in progress.

Discussion. The number of recipients on the waiting list and the number of performed organ transplants increases every year around the world [3]. According to the results of the UNOS registry database report for 2022, 42,800 organs were transplanted in the USA (which is a record for the last 12 years), of which 25,000 were kidney transplants and 4,111 - heart transplants. According to the Eurotransplant, 7,183 organ transplants were performed in Europe in 2022, to include 4,201 isolated kidney transplants and 644 heart transplants. The frequency of multi-organ transplants is also increasing. UNOS data for 2020-2021 reports that heart-kidney transplants were performed in 736 cases, heart-lung transplants in 116 cases, heart-liver transplants, etc. in 102 cases [13].

The number of heart transplants in the US has increased by 67%, from 2,199 in 2000 to 4,111 in 2022. In particular, combined heart and kidney transplants increased by 750%, from 29 in 2000 to 401 in 2021.

Despite the rapid growth of both single and combined transplants, selection criteria for performing multi-organ transplants remain poorly defined and vary by geographic region and local protocols [8,9].

Based on the study of Krishna A. et al., 1507 simultaneous heart and kidney transplants were analysed and grounds for combined transplantation were established. Regarding the heart, the criterion to select the recipient was progressing heart failure resulting from cardiomyopathy: dilated (45%), ischaemic (43.3%), restrictive (4%), arrhythmogenic (3.7%), congenital heart defects (1.7 %). For kidneys, the main indications for transplantation were the presence of the terminal stage of CKD with an estimated glomerular filtration rate <37 mL/min, and the presence of "dialysis dependence", which Gill and colleagues proposed to use as a criterion for combined organ transplantation [8,14].

However, there are no reports on combined heart and kidney transplantation in patients with calcific heart disease.

Due to the lack of generally accepted recommendations, there are ongoing discussions regarding the phasing of combined transplants. Some authors [5, 15] believe that in order to avoid haemodynamic instability and its negative impact on the stage of kidney implantation and early post-transplantation period, it would be advisable to carry out a staged transplantation, bearing in mind the postponement of the implantation of the donor kidney for several hours. However, according to Debout A and Wong G, staged intervention increases the time of graft ischaemia and is associated with impaired renal function with the development of primary graft dysfunction and a decrease in long-term graft survival, so they recommended performing the kidney transplantation immediately after closing the chest [16, 18]. We agree with Debout A and Wong G and performed kidney implantation immediately after chest closure. We believe that, on the one hand, this approach allows reducing the time of the graft ischemia, and on the other - reducing the duration of surgical intervention, which in turn should have a favourable effect on the course of the post-surgery period.

The question of the causes of the development of acute renal failure of the transplant in early post-surgery period remains open as well. One of the latest publications from the UNOS database shows that 26% of those who underwent a one-stage heart and kidney transplant experience acute graft failure within the first 30 days, requiring haemodialysis sessions [3]. The authors note that the major role in the development of this complication is played by the massive immunosuppressive therapy, and especially the use of calcineurin inhibitors, which are nephrotoxic. On the other hand, it was established that patients, whose preoperative GFR was less than 30 mL/min and were on systemic haemodialysis for a long time, will foreseeably require haemodialysis in early post-surgery period [8]. In our observation, the development of acute renal failure of the graft started in early post-surgery period and was successfully treated by intermittent renal

replacement therapy sessions for 1 week.

The presented clinical supervision is the first experience of multi-organ transplantation in Ukraine.

Our clinical supervision demonstrates the feasibility of successful simultaneous orthotopic heart and kidney transplantation and demonstrates encouraging immediate and medium-term follow-up results.

We believe that careful selection of recipients and donor organs, assessment of the risks and benefits of combined transplantation and the presence of a multidisciplinary team are the keys to achieving the best results. This issue requires a more detailed study and assessment of long-term results.

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КЛИНИЧЕСКИЙ РЕЗУЛЬТАТ ОДНОВРЕМЕННОЙ ТРАНСПЛАНТАЦИИ СЕРДЦА И ПОЧКИ ОТ ОДНОГО ДОНОРА (случай из клинической практики)

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Резюме. Количество реципиентов в листе ожидания и количество проведенных трансплантаций органов увеличивается с каждым годом во всем мире. Несмотря на быстрый рост как одиночных, так и комбинированных трансплантаций, критерии выбора для выполнения трансплантации нескольких органов остаются плохо определенными и варьируются в зависимости от географического региона и местных протоколов. Представленное в статье клиническое наблюдение демонстрирует возможность успешной одновременной ортотопической трансплантации сердца и почки и демонстрирует обнадеживающие ближайшие и среднесрочные результаты наблюдения.

Больной П., 51 год, с выраженным кальцинозом митрального клапана с вовлечением задне-боковой стенки левого желудочка, не поддающимся хирургической коррекции, и терминальной стадией хронической болезни почек, выполнена ортотопическая одномоментная трансплантация сердца и почки. Ранний послеоперационный период осложнился развитием острой почечной недостаточности трансплантата, что было купировано курсами гемодиализа.

Представленное клиническое наблюдение является первым опытом мультиорганной трансплантации в Украине.

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