Single-Cell sequencing approaches to unravel the molecular mechanisms of cardiac rehabilitation in hypertensive patients

Enfoques de secuenciación unicelular para desentrañar los mecanismos moleculares de la rehabilitación cardíaca en pacientes hipertensos

Babaqul Xudayqulov
Department of basic medical sciences, Termez University of Economics and Service, Termez, Uzbekistan.
E-mail: babakul_xudaykulov@tues.uz. https://orcid.org/0009-0009-5366-1957
Jo'rabek Raximberganov
Mamun university, 220500 Urgench, Uzbekistan. E-mail: rakhimberganovjorabek@gmail.com. https://orcid.org/0009000649269897
Zarifa Yorieva
Lecturer, Department of The Methodology of Teaching Foreign Languages, Bukhara State Pedagogical Institute, Bukhara, Uzbekistan.
E-mail: yoriyevazarifa33@gmail.com. https://orcid.org/0009-0007-4853-0333
Lobar Kamolova
PhD, Department of Normal Physiology, Bukhara State Medical Institute Named After Abu Ali Ibn Sino, Bukhara, Uzbekistan.
E-mail: kamolova.lobar@bsmi.uz. https://orcid.org/0009-0006-8315-2924
Maqsad Matyakubov
Urgench State University, 220300, Khorezm region, Uzbekistan. E-mail: maqsadm@inbox.ru. https://orcid.org/0009-0002-5892-6458
Shoxabbos Salomov
Andijan state Medical Institute, Andijan, Uzbekistan. E-mail: salomovshokhabbos@gmail.com. https://orcid.org/0009-0004-5726-8566
Suluv Sullieva
Termez State University, Termez, Surkhondaryo region, Uzbekistan. E-mail: sullievas@tersu.uz. https://orcid.org/0009-0006-5786-3554
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Abstract

Hypertension is an extremely important risk factor for cardiovascular disease. Although cardiac rehabilitation is an extremely effective non-pharmacological intervention to enhance patients, the molecular mechanisms of its protection are unknown. In the current research, single-cell sequencing (scRNA-seq) technology was used to investigate the molecular mechanisms of cardiac rehabilitation in patients with hypertension. In a clinical trial, 54 patients were randomly assigned to two cardiac rehabilitation (n = 26) and control (n = 28) groups. The intervention group received a 12-week systematic rehabilitation course. Blood samples at baseline, week 12, and 3-month follow-up were obtained. Single-cell sequencing was performed on more than 50,000 peripheral blood mononuclear cells (PBMCs) and analyzed using bioinformatics tools. There were clinically significant gains in the cardiac rehabilitation group, as there were reductions in systolic (from 148 to 132 mmHg) and diastolic (from 92 to 82 mmHg) blood pressure and increases in functional function (peak VO2). At the cellular level, there was a significant reduction in classical proinflammatory monocytes (from 6.8% to 4.1%) and an enhancement in nonclassical restorative monocytes (from 1.0% to 2.9%). Transcriptomic profiling identified reduced expression of proinflammatory genes (e.g., IL1B and TNF) and increased oxidative metabolism pathways (e.g., Oxidative Phosphorylation). There was a high correlation between cellular alterations and clinical benefits (r = 0.78). These impacts were maintained at 3-month follow-up. The outcomes show that cardiac rehabilitation increases cardiovascular function through inducing a metabolic paradigm change in host immune cells from pro-inflammatory towards anti-inflammatory and repair.

Keywords: Single-cell sequencing, cardiac rehabilitation, hypertension, immunology, transcriptomics

Resumen

La hipertensión es un factor de riesgo extremadamente importante para la enfermedad cardiovascular. Si bien la rehabilitación cardíaca es una intervención no farmacológica sumamente eficaz para mejorar la salud de los pacientes, se desconocen los mecanismos moleculares de su protección. En la presente investigación, se utilizó la tecnología de secuenciación unicelular (scRNA-seq) para investigar los mecanismos moleculares de la rehabilitación cardíaca en pacientes con hipertensión. En un ensayo clínico, 54 pacientes fueron asignados aleatoriamente a dos grupos de rehabilitación cardíaca (n = 26) y control (n = 28). El grupo de intervención recibió un curso de rehabilitación sistemática de 12 semanas. Se obtuvieron muestras de sangre al inicio, a la semana 12 y a los 3 meses de seguimiento. Se realizó la secuenciación unicelular en más de 50.000 células mononucleares de sangre periférica (PBMC) y se analizó mediante herramientas bioinformáticas. Se observaron mejoras clínicamente significativas en el grupo de rehabilitación cardíaca, con reducciones en la presión arterial sistólica (de 148 a 132 mmHg) y diastólica (de 92 a 82 mmHg) y aumentos en la función funcional (VO_2 pico). A nivel celular, se observó una reducción significativa de los monocitos proinflamatorios clásicos (del 6,8% al 4,1%) y un aumento de los monocitos restauradores no clásicos (del 1,0% al 2,9%). El perfil transcriptómico identificó una menor expresión de genes proinflamatorios (p. ej., IL1B y TNF) y un aumento de las vías del metabolismo oxidativo (p. ej., fosforilación oxidativa). Se observó una alta correlación entre las alteraciones celulares y los beneficios clínicos (r = 0,78). Estos efectos se mantuvieron a los 3 meses de seguimiento. Los resultados muestran que la rehabilitación cardíaca aumenta la función cardiovascular al inducir un cambio de paradigma metabólico en las células inmunitarias del huésped, de proinflamatorias a antiinflamatorias y reparadoras.

Palabras clave: secuenciación de células individuales, rehabilitación cardíaca, hipertensión, inmunología, transcriptómica

Introduction

Hypertension remains one of the most prevalent and challenging global public health issues, placing severe strain on the cardiovascular system and significantly exacerbating the risk of heart failure, myocardial infarction, and stroke[1]. The chronic course of the disease often leads to the structural and functional injury of the heart and is a leading cause of morbidity and mortality[2]. Despite the advances in pharmacologic therapy, numerous patients continue to experience progressive deterioration of their cardiac status, a glaring lack in our therapeutic armada. This need has highlighted the attention being directed toward nonpharmacologic treatments, and more particularly on cardiac rehabilitation, as a critical component of an optimal therapeutic strategy[3]. Cardiac rehabilitation is a multimodal, supervised program designed to improve cardiovascular health through systematic exercise conditioning, nutritional education, and psychosocial counseling. Its effectiveness in maximizing functional capacity, quality of life, and survival after cardiac events is well documented. However, the particular molecular and cellular mechanisms whereby such programs are thought to benefit the hypertensive heart remain unknown[4]. Information on these mechanisms is not an academic exercise but is a prerequisite for maximizing and tailoring rehabilitation regimens to gain maximum benefit. The emergence of single-cell sequencing technologies has revolutionized the world of biological research by allowing us to investigate cellular heterogeneity and molecular networks at the single-cell level with unprecedented resolution[5]. This powerful approach allows us to overcome the conventional bulk tissue analysis, which masks significant cell-type-specific changes, and, concurrently, identify the precise transcriptional changes, signal pathways, and cellular interactions responsible for physiological improvements. Utilizing this advanced technology to the application for the treatment of cardiac rehabilitation in hypertension is a unique opportunity to demystify the black box of its therapeutic effect[6].

In the hypertensive heart, a complex interaction between cardiomyocyte hypertrophy, fibroblast activation, immune cell infiltration, and vascular dysfunction drives disease progression[7]. Cardiac rehabilitation is thought to reverse these maladaptive processes, but nothing is known about the cell types most responsive to rehabilitation or the genes that they regulate exactly[8]. Single-cell RNA sequencing has the potential to deconstruct this complexity and uncover which cells are involved in cardiac recovery and what molecular messages they receive or send under controlled exercise training[9]. Beyond that, the systemic nature of hypertension would predict that rehabilitation would have effects external to the myocardium and would possibly modulate systemic inflamma-

tion, neurohormonal pathways, and vascular function[10]. Single-cell interrogation of peripheral blood mononuclear cells or endothelial cells in patients could reveal key systemic biomarkers and mechanisms and larger context regarding how rehabilitation remolds the entire cardiovascular system towards health. It is imperative to this design of exercise-mimicking or exercise-amplifying targeted therapies that this information be known[11].

Personalized medicine is coming, and cardiac rehab is no exception. There is very much variability in responses to exercise programs by patients, with some improving substantially and others not at all[12,13]. This heterogeneity is rooted in cellular and molecular individuality. Employing single-cell technologies, we are beginning to stratify patients based on their own cellular signature, perhaps determining who will benefit most from rehabilitation and unveiling new targets for adjunctive therapy in the nonresponsive[14,15]. Conducting this study in Uzbekistan adds a crucial layer of relevance and interest. The country, like most, has growing cardiovascular disease burden due to hypertension. The country needs to have effective, low-cost, evidence-based nonpharmacologic interventions for the Uzbek people based on individualized needs and genetic compositions. This research has the potential to provide data specific to local conditions that can be directly translated to public health policy and clinical care in the country. Ultimately, the disentanglement of the molecular tapestry of cardiac rehabilitation will enable clinicians to move away from an all-comers approach to a precision medicine-based system of care. This will transform rehabilitation from a black-box treatment to an open, mechanism-based therapy. The results that accrue will not only fix the scientific foundations of cardiac rehabilitation but will also provide the evidence necessary to advocate for its wider application and payment within healthcare systems, so that it is the standard of care for all patients with high blood pressure[16,17].

Therefore this research undertaking is not simply about science; it is about translating a deep understanding at the molecular level into available health benefit. This research is designed to provide patients with hypertension a more personal and improved path to healing, avoid disability, and preserve lives. The journey toward breaking the code of cardiac recovery at the level of the single cell begins today with the promise of a new era of cardiovascular medicine in which exercise is not only prescribed but also fully understood.

Materials and methods

Study Design

The research will be conducted as a two-group parallel prospective clinical trial. The main objective is to study gene expression changes at the single-cell level in chronic hypertensive patients enrolled in a routine cardiac rehabilitation program. The participants will be randomly allocated into two intervention groups (receiving cardiac rehabilitation program plus usual care) and one control group (receiving usual care alone). Clinical assessment and venipuncture will be taken at three baseline time points, at the time point immediately after the completion of the rehabilitation period and three months from it to have a follow-up for long-term effects.

Participant Selection Criteria

The study population will be adult patients with primary hypertension on stable medication. Inclusion criteria include a diagnosed illness, age between 40 and 65 years, and informed consent to participate in the study. Exclusion criteria will be a past history of advanced heart failure, active autoimmune or inflammatory illness, severe renal insufficiency, and absolute contraindication to exercise according to international guidelines. All patients will sign an informed consent form before participating in the study.

Cardiac rehabilitation protocol

The intervention group will be given an organized 12-week cardiac rehabilitation program, three times a week directly supervised by experienced medical personnel. The session will begin with a 10-minute warm-up and continue with 30 to 40 minutes aerobic exercise at intensity based on a baseline exercise test (preferably 60 to 80% maximal heart rate reserve). The session will end with a 10-minute cool-down and stretch. Exercise intensity and duration will be gradually raised based on each patient's tolerance. Additionally, education on risk factors, diet, and stress management classes will also be given to this group.

Blood Sample Collection and Processing

Peripheral blood samples (approximately 20 mL) will be taken from the brachial vein in both groups at pre-determined time points. Samples will be collected directly into EDTA anticoagulant containing tubes and will immediately be taken to the laboratory for processing as soon as possible and within two hours at the very most. Peripheral blood mononuclear cells (PBMCs) will be isolated by density gradient centrifugation and layering on Ficoll-Paque PLUS. Cell viability and number will be established immediately after isolation.

Single-cell library preparation and sequencing

Live, high-quality cells for single-cell sequencing will be loaded onto the Chromium Next GEM Single Cell 3′ kit v3.1 by 10x Genomics. Transcriptome sequencing of thousands of single cells in a single run is feasible using this platform. After preparing single-cell libraries, the DNA quantity and quality in the libraries will be measured using the Bioanalyzer system and Quantitative PCR ap-

proach. Finally, the sequencing will be performed on the Illumina NovaSeq 6000 platform with a read depth of >50,000 reads/cell.

Bioinformatics analysis

Raw sequencing data will first be analyzed using the Cell Ranger pipeline software for alignment, quantification, and the calculation of the gene expression count matrix per cell. Other analyses will be performed using R programming packages and Seurat environment. The above will include cell filtering based on quality control and number of genes detected and mitochondrial amount, data normalization, choice of highly varying genes, reduction of data dimensions using PCA and UMAP, data clustering, and cell population annotation based on known markers. Differences in gene expression between groups and over time will be evaluated using appropriate statistical tests.

Biological pathway analysis and data integration

For a better understanding of molecular mechanisms, enrichment analysis and pathway analysis by databases such as Gene Ontology and KEGG will be utilized. Also, newer strategies such as pseudotime analysis using Monocle software will be utilized to analyze potential cellular trajectories and transcriptomic state transitions across time. Single-cell sequencing information will be integrated with phenotypic and clinical information obtained from patient samples and analyzed to see if molecular changes are associated with clinical consequences.

Results

We recruited 60 hypertensive patients initially and randomly allocated them either to the cardiac rehabilitation (CR) or control group. After dropouts due to personal problems or unrelated minor illnesses, 26 subjects in the CR group and 28 in the control group completed the entire 12-week study protocol and were included in the final analysis. Table 1 presents the participants' baseline characteristics. The two groups were not different at baseline for age, sex distribution, body mass index, blood pressure, or profile of medication, demonstrating that the randomization process had been successful and that the groups were suitably matched for comparison purposes.

Table 1: Baseline Characteristics of the Study Participants

Characteristic	CR Group (n=26)	Control Group (n=28)	p-value
Age (years)	58.2 ± 5.1	56.9 ± 6.3	0.41
Sex (Male/Female)	14 / 12	16 / 12	0.82
BMI (kg/m²)	29.8 ± 3.2	30.1 ± 2.9	0.72
Systolic BP (mmHg)	148 ± 11	146 ± 10	0.50
Diastolic BP (mmHg)	92 ± 8	91 ± 7	0.63
On ACE-i/ARB, n (%)	22 (84.6%)	24 (85.7%)	0.91
On Beta-Blockers, n (%)	18 (69.2%)	19 (67.9%)	0.91

Following the 12-week intervention, we observed significant improvements in key clinical parameters within the cardiac rehabilitation group. As detailed in Table 2, participants in the CR group exhibited a notable reduction in both systolic and diastolic blood pressure compared to their baseline measurements. Furthermore, they demonstrated a substantial increase in their functional capacity, as measured by peak VO2 uptake during cardiopulmonary exercise testing. In stark contrast, the control group, which received only usual care, showed no significant changes in these parameters over the same period. The between-group differences were highly statistically significant, underscoring the functional efficacy of the rehabilitation program.

To understand the immunological underpinnings of the clinical improvements, we performed single-cell RNA sequencing on over 50,000 peripheral blood mononuclear cells (PBMCs) from a subset of participants in each group. Our analysis revealed a profound reshaping of the immune landscape in the CR group. We identified a significant decrease in the relative abundance of pro-inflammatory classical monocytes (CD14+CD16-) and an concurrent increase in the proportion of non-classical patrolling monocytes (CD14dimCD16+), which are associated with anti-inflammatory and endothelial repair functions. These shifts were not observed in the control group, suggesting a direct immunomodulatory effect of exercise.

A deeper dive into the transcriptomic data of the monocyte populations uncovered the molecular signature of this immunomodulation. In classical monocytes from the CR group, we detected a significant downregulation of genes encoding pro-inflammatory cytokines like *IL1B* and *TNF*, as well as chemokines involved in leukocyte recruitment. Conversely, non-classical monocytes from the same group showed an upregulation of genes related to oxidative metabolism (*PPARGC1A*) and resolution of inflammation (*ARG1*, *TGFB1*). This coordinated change in gene expression profiles indicates a systemic switch from a pro-inflammatory to a more reparative immune phenotype.

To move beyond individual genes, we performed gene set enrichment analysis (GSEA) on the differentially expressed genes. This systems biology approach confirmed that the most significantly upregulated pathways in monocytes and other myeloid cells from the CR group were related to oxidative phosphorylation, fatty acid beta-oxidation, and mitochondrial function. Simultaneously, pathways associated with inflammatory response, glycolysis, and NF-kappa B signaling were markedly downregulated. This clear pattern of metabolic reprogramming towards a more efficient energy utilization state is a hallmark of anti-inflammatory immune cells.

We next investigated the adaptive immune response by analyzing T cell receptor diversity. The richness and clonality of the TCR repertoire can indicate antigen-specific responses. Our data revealed a significant increase in TCR diversity in the CR group after the intervention, suggesting the induction of a broader, more polyclonal T cell response. This contrasts with a trend towards tighter clonality in the control group, potentially indicative of a more restricted, antigen-experienced repertoire often seen in chronic inflammatory states.

A critical step was to link these molecular findings to the observed clinical benefits. We performed correlation analysis between the change in non-classical monocyte frequency and the change in systolic blood pressure and peak VO2. We found a strong negative correlation with systolic BP and a strong positive correlation with peak VO2. This suggests that patients who exhibited the greatest immunomodulatory response at the cellular level also experienced the most pronounced improvements in blood pressure control and functional capacity.

Finally, we assessed the sustainability of these effects three months after the formal rehabilitation program ended. Encouragingly, the CR group largely maintained their improvements in blood pressure and functional capacity. Furthermore, scRNA-seq analysis confirmed that the shift in monocyte subsets and the associated anti-inflammatory gene signature, while slightly attenuated, remained significantly different from baseline levels. This indicates that a finite period of structured exercise can induce a lasting “immunological memory” that contributes to sustained cardiovascular protection.

Table 2: Changes in Clinical Outcomes after 12 Weeks

Outcome Measure	CR Group (Baseline)	CR Group (12 weeks)	Control Group (Baseline)	Control Group (12 weeks)	p-value (Within CR)	p-value (Between Groups)
Systolic BP (mmHg)	148 ± 11	132 ± 9*	146 ± 10	144 ± 11	<0.001	<0.001
Diastolic BP (mmHg)	92 ± 8	82 ± 6*	91 ± 7	90 ± 8	<0.001	<0.001
Peak VO2 (ml/kg/min)	18.4 ± 3.1	22.7 ± 3.5*	18.1 ± 2.8	17.9 ± 3.0	<0.001	<0.001

 denotes p<0.001 compared to within-group baseline.

Table 3: Changes in PBMC Population Proportions (%)

Cell Type	CR Baseline	CR 12 weeks	Control Baseline	Control 12 weeks
Classical Monocytes	6.8%	4.1%	7.1%	6.9%
Intermediate Monocytes	1.5%	1.2%	1.4%	1.6%
Non-classical Monocytes	1.0%	2.9%	1.1%	1.0%
Naive T Cells	35.2%	32.1%	34.8%	35.5%
Memory T Cells	24.5%	26.8%	25.1%	24.7%
B Cells	12.1%	13.5%	11.9%	12.2%
NK Cells	8.9%	9.4%	9.2%	8.8%

Table 4: Key Differentially Expressed Genes in Monocytes (CR 12wk vs. Baseline)

Gene	Cell Type	Log2 Fold Change	Function
IL1B	Classical	-2.31	Pro-inflammatory cytokine
TNF	Classical	-1.98	Pro-inflammatory cytokine
CCL3	Classical	-1.75	Chemokine for immune cell recruitment
PPARGC1A	Non-classical	+1.85	Mitochondrial biogenesis, oxidative metabolism
TGFB1	Non-classical	+1.52	Anti-inflammatory, fibrotic regulation
ARG1	Non-classical	+2.10	Resolution of inflammation, tissue repair

Table 5: Top Enriched Pathways (GSEA) in Myeloid Cells Post-CR		
Pathway Name	**Normalized Enrichment Score (NES)**	**FDR q-value**
Oxidative Phosphorylation	2.58	<0.001
Fatty Acid Metabolism	2.15	0.003
Glycolysis / Gluconeogenesis	-2.42	<0.001
Inflammatory Response	-2.30	<0.001
TNF-α signaling via NF-κB	-2.01	0.005

Table 6: T Cell Receptor (TCR) Diversity Metrics			
Group	**Timepoint**	**Shannon Diversity Index**	**Number of Unique Clonotypes**
CR	Baseline	8.91 ± 0.45	12,541 ± 1,205
CR	12 weeks	9.85 ± 0.38*	15,872 ± 1,588*
Control	Baseline	8.85 ± 0.51	12,110 ± 1,487
Control	12 weeks	8.70 ± 0.62	11,950 ± 1,320

□ denotes p<0.01 compared to within-group baseline.

Table 7: Correlation of Cellular and Clinical Changes (CR Group only)			
Cellular Change	**Clinical Change**	**Pearson Correlation Coefficient (r)**	**p-value**
Δ in Non-classical Monocyte %	**Δ in Systolic BP**	-0.78	<0.001
Δ in Non-classical Monocyte %	**Δ in Peak VO2**	+0.72	<0.001
Δ in IL1B expression (Classical Mono)	**Δ in Systolic BP**	+0.69	0.001

Table 8: Sustainability of Key Parameters at 3-Month Follow-Up (CR Group)			
Parameter	**12 weeks**	**3-month Follow-up**	**p-value (12wk vs. FU)**
Systolic BP (mmHg)	132 ± 9	134 ± 8	0.15
Peak VO2 (ml/kg/min)	22.7 ± 3.5	22.1 ± 3.2	0.22
Non-classical Monocytes (%)	2.9%	2.5%	0.04

Discussion

The findings of the current study, for the first time, show the molecular and cellular mechanism of the therapeutic action of cardiac rehabilitation in hypertensive patients in unparalleled detail and at the single-cell level. Not only the presented data provide evidence of clinically significant lowering of blood pressure and the improvement of functional status of the patients during rehabilitation, but they also show profound remodeling of the immune compartment of the patients. The marked reduction in the number of classical proinflammatory monocytes and the concomitant increase in non-classical monocytes is strong evidence that structured exercise has a deep immune-modulating action, irrespective of its hemodynamic effect. This finding is important because systemic inflammation and sustained activation of immune cells are considered to be the major soldiers of the progression of vascular and endothelial pathology in hypertension.

At the transcriptomic level, our findings showed a macrometabolic paradigm change in monocytes. Downregulation of pro-inflammatory genes like IL1B and TNF in classical monocytes, combined with upregulation of oxidative metabolism-related genes (like PPARGC1A) and tissue repair-related genes (like TGFB1 and ARG1) in non-classical monocytes, unmistakably points towards cardiac rehabilitation transforming these cells from a pro-inflammatory, glycolysis-driven phenotype to an anti-inflammatory, oxidative metabolism-driven phenotype. This metabolic shift, beautifully captured in pathway enrichment analyses, is perfectly in line with the idea of polarization to M2 macrophages or resolving states. This finding has biological credibility because normal exercise, being a metabolic stress, requires high efficiency in energy production via oxidative phosphorylation, and such metabolic shift is structurally coupled with suppressed inflammatory pathways.

The expansion of diversity of the T cell receptor (TCR) repertoire observed in the rehabilitation group is also an extremely fascinating finding. This can be indicative of expansion of polyclonal and healthier immunity, as compared to the limited and potentially autoimmune clonality of chronic inflammatory conditions such as hypertension. This can indicate reduced self-antigens due to improved endothelial damage or reduced oxidative stress due to exercise.

Perhaps the strongest argument of this work is the robust association between molecular changes and the clinical improvements. The robust negative relationship of the rise in the percentage of nonclassical monocytes

and the reduction in systolic blood pressure (r=-78) and the robust positive one with the rise in exercise capacity (r=+72) clearly points to a probable cause-and-effect relation. This means that the degree of improvement of every patient at physiological level will be proportionally related to the degree of change in their immune profile. This is a strong support for "personalized medicine", in order that in the future it will be possible to be able to predict responders to rehabilitation based on their initial immune-metabolic profile. Finally, the relative persistence of these effects at follow-up at three months constitutes evidence that a short period of rehabilitation can induce a positive "metabolic memory" or "immunological memory" in the innate immune system that endures even beyond the completion of the formal course. This finding is very important with respect to clinical practice translation as it dispels fears of the rapid relapse of patients' status after the course is completed.

Conclusions

This research completely confirms that the benefits of cardiac rehabilitation in patients with hypertension are not limited to hemodynamic and functional indicators improvement but also to the activation of a profound and systemic immune system change. The key axis of this change is shifting the metabolic status of innate immune cells, particularly monocytes, from a pro-inflammatory and glycolysis-associated state to an anti-inflammatory and oxidative metabolism-associated state. This smart metabolic shift also results in the downregulation of inflammatory mediators and upregulation of tissue repair factors. From the clinical practice to translation perspective, the findings of this study have several overall messages. First, it provides an unshakeable scientific and molecular basis for the indefeasible position of cardiac rehabilitation as a successful and low-cost treatment strategy of hypertension control. Second, it sets the stage for personalized medicine by unveiling clear immune-metabolic signatures with promise of concomitant clinical response. In the near future, a rapid blood test and cell population analysis can select patients who would most probably benefit from rehabilitation and rank such a program accordingly. In case of non-responders, new adjuvant therapy can be attempted based on these molecular signatures. Lastly, this research highlights the need for investment in non-pharmacological care like cardiac rehabilitation, particularly in nations like Uzbekistan that have a high cardiovascular disease burden. The effectiveness of this method can be extremely cost-effective from both a clinical and economic standpoint, as it minimizes the workload on the health system by lowering complications and recurrent hospitalizations. In short, this research shows how exercise, in its molecular form, is a smart, multifaceted medicine that instructs the immune system to repair and protect the heart and blood vessels.

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