New Hypothesis in Clinical Medicine

Functional Recovery of a Human Neonatal Heart After Severe Myocardial Infarction

Bernhard J. Haubner1,3, Johanna Schneider2, Ulrich Schweigmann2, Thomas Schuetz3, Wolfgang Dichtl3, Corinna Velik-Salchner4, Joerg-I. Stein2, Josef M. Penninger1

1 IMBA, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Dr. Bohrgasse 3, 1030 Vienna, Austria; 2Department of Pediatrics III - Cardiology, Pulmonology, Allergology, Cystic Fibrosis, Medical University of Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria; 3Department of Internal Medicine III (Cardiology), Medical University of Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria; 4Department of Anesthesia and Intensive Care, Medical University of Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria.

Running title: Human Neonatal Myocardial Infarction

B.J.H. and J.S. contributed equally to this work.

Subject Terms:
Congenital Heart Disease
Myocardial Infarction
Myocardial Regeneration
Pediatrics
Translational Studies

Address correspondence to:
Dr. Joerg-I. Stein
Department of Paediatrics III
Cardiology, Pulmonology, Allergology, Cystic Fibrosis
Medical University of Innsbruck
Anichstr. 35
6020 Innsbruck
Austria
Joerg.Stein@i-med.ac.at

Dr. Josef M. Penninger
Institute of Molecular Biotechnology of the Austrian Academy of Sciences
Dr. Bohrgasse 3
1030 Wien
Austria
Tel: +43 1 790 44 4702
Fax: +43 1 790 44 110
josef.penninger@imba.oeaw.ac.at

In November 2015, the average time from submission to first decision for all original research papers submitted to Circulation Research was 15.52 days.
ABSTRACT

Rationale: Cardiac remodeling and subsequent heart failure remain critical issues after myocardial infarction despite improved treatment and reperfusion strategies. Recently, cardiac regeneration has been demonstrated in fish and newborn mice following apex resection or cardiac infarctions. Two key issues remain to translate findings in model organisms to future therapies in humans: what is the mechanism and can cardiac regeneration indeed occur in newborn humans?

Objective: To assess whether human neonatal hearts can functionally recover following myocardial infarction.

Methods and Results: Here, we report the case of a newborn child suffering from a severe myocardial infarction due to coronary artery occlusion. The child developed massive cardiac damage as defined by serum markers for cardiomyocyte cell death, electrocardiograms, echocardiography, and cardiac angiography. Remarkably, within weeks after the initial ischemic insult, we observed functional cardiac recovery, which translated into long-term normal heart function.

Conclusions: These data indicate that, similar to neonatal rodents, newborn humans might have the intrinsic capacity to repair myocardial damage and completely recover cardiac function.

Keywords: Cardiac regeneration, myocardial infarction, pediatric cardiology.

Nonstandard Abbreviations and Acronyms:

MI myocardial infarction
ECG electrocardiography or electrocardiogram
LAD left anterior descending artery
ECMO extracorporeal membrane oxygenation
INTRODUCTION

Despite significant improvements in prevention and therapies, the burden of myocardial infarction (MI) remains high.1 Recent advances in the treatment of the disease have resulted in marked improvement in the initial survival of patients. However, many patients develop heart failure because the initial loss of cardiomyocytes cannot be compensated, resulting in tissue remodeling and functional deterioration of the heart.² Although there have been great advances in the understanding of heart failure in recent decades and acute treatment of heart attacks has markedly improved survival, one key issue for human health is how to effectively regenerate the heart after injury.

Major efforts are underway to develop strategies for myocardial recovery and thus improve cardiac morbidity and mortality, including (stem) cell based therapies,¹⁴ transdifferentiation of non-cardiomyocytes into cardiomyocytes,⁶,⁷ or to stimulate the intrinsic regenerative potential.⁸-¹¹ However, the fact remains that lost myocardium can still not be effectively regenerated in human patients.¹²,¹³ Pioneering experiments demonstrated that fish can completely regenerate the heart following resection of the heart apex,¹⁴ spurring a plethora of studies using fish as a model organism.¹⁵,¹⁶ Whereas axolotls¹⁷ and zebrafish¹⁴ have the potential of lifelong myocardial recovery, it has been recently shown that newborn mice, but not mice beyond one week of age, can regenerate the cardiac apex following resection.¹⁸ However, this apex resection model has been recently questioned.¹⁹ Moreover our group and Olson’s group have recently reported complete morphologic and functional cardiac repair in newborn mice following severe myocardial infarction.²⁰,²¹ Besides the elucidation of the underlying mechanism for neonatal cardiac repair,²² one key question remains: “Can we translate these models to the human heart considering fundamental differences in basic cardiac physiology?” Here, we report the case of severe myocardial infarction in a newborn child and provide evidence of complete functional cardiac recovery in human.

METHODS

Clinical assays were performed following standard protocols and are described in the online supplement.

RESULTS

A 27 years old woman gave vaginal birth to a boy at the end of the 39th gestation week. No complications were observed throughout the pregnancy and no morphological or functional irregularities were evident in the developing fetus as determined by transabdominal ultrasound and cardiotocography. The labor was uneventful, further supported by the normal values of the umbilical cord arterial blood. However, the newborn manifested severe cyanosis and oxygen saturation was markedly decreased. Despite ventilation therapy, no improvement of the child’s health was achieved leading to examination of the heart and immediate referral to our pediatric center (Online figure IA).

Initial examination using electrocardiography (ECG) revealed signs of acute myocardial ischemia (Figure 1A). Echocardiography showed severely impaired left ventricular function with abnormal regional wall contractions (Figure 1B). The cardiac biomarker proteins troponin T and creatine kinase, both clinical markers of myocardial damage,²³ were massively increased within hours after birth (Figure 1C/D). Moreover, we detected increased levels of NTproBNP (Online figure IB), a well-established marker of elevated intracardiac pressure.²⁴ Of note, troponin T is released from dying cardiomyocytes and directly correlates with the extent of cardiomyocyte necrosis.²⁵ In our patient we found troponin T serum levels close to 15000ng/L (Figure 1C), levels that are even higher than in very severe cases of myocardial infarction.
infarctions in the adult. Thus, all these parameters show that the newborn child had suffered severe cardiac injury.

To determine the cause of myocardial damage, we performed Doppler echocardiography. We observed a block in blood flow in the left anterior descending artery (LAD) (Figure 2A), indicative of occlusion of this key coronary blood vessel. To directly demonstrate LAD obstruction, we performed cardiac angiography. We indeed observed a complete thrombotic occlusion of the proximal LAD without any detectable collateral blood flow (Figure 2B). No obvious cause for thrombus formation could be identified, e.g. there was no enhanced coagulation and illicit drug abuse of the mother was excluded. The child developed acute left ventricular heart failure necessitating inotropic therapy and the implantation of an extracorporeal membrane oxygenation (ECMO) device (Online figure IA). Intravenous thrombolysis was initiated ~ 28 hours after the first symptoms. Importantly, Doppler echocardiography as well as repeated angiography showed reopening of the occluded LAD lesion (Figure 2A+B). Despite re-establishment of coronary blood flow, the child continued to present with myocardial damage as evidenced by anteroseptal edema and regional hypokinesis at the area of infarction (Figure 3A+B online videos I and II). Moreover, following thrombolysis, we detected pathological ECG Q-waves (Figure 3C), further supporting myocardial damage. Thus, the newborn suffered from LAD occlusion for more than 20 hours resulting in massive myocardial infarction.

The following sub-acute phase was characterized by continuous cardiac improvement without any complications. All serum markers for cardiac damage, i.e. troponin T and creatine kinase, rapidly returned to normal levels (Figure 4A). Moreover, NTproBNP serum level returned to background levels (Figure 4B). In line with normalized NTproBNP levels, cardiac function, i.e. fractional shortening and ejection fractions, markedly improved to levels observed in age-matched, healthy normal children (Figure 4C+D). The child was discharged one and a half months after birth with apparently normal heart parameters. The patient was followed up on a regular basis for up to one year; and the boy’s development was indistinguishable to age-matched healthy babies (Online figure IIA). Neither morphological nor neurological deficits were found up to his first birthday. Most importantly at one year of age, echocardiography and NTproBNP evaluations showed normal cardiac morphologies and heart function (Figure 4B+C, and Online figure IIA and IIB). Thus, based on all available evidence this child had no apparent signs of any structural heart abnormalities and completely recovered cardiac function.

**DISCUSSION**

We present the case of a newborn patient with severe anteroseptal ST elevation myocardial infarction, confirmed by multiple assays such as angiography, ECG, echocardiography, and increased cardiac serum biomarkers. Amazingly, the patient’s heart rapidly recovered despite very late thrombolytic reperfusion therapy and was indistinguishable in function and morphology to hearts of comparable 1-year-old infants. Of note, a few case reports have been published describing patients suffering from myocardial infarction in the neonatal period without structural heart disease. All reported newborns with documented myocardial infarction that survived the acute phase apparently recovered their heart function. Since reperfusion therapy was successfully performed in our patient we cannot exclude the phenomena of stunning or hibernation contributing to the profound cardiac improvements in our patient. However, delayed thrombolysis, massive release of cardiomyocyte-specific troponin T, indicative of cardiomyocyte necrosis, and ECG- and echocardiography-documented myocardial damage all clearly indicate that the newborn child had suffered from severe myocardial infarction with subsequent severe structural and functional cardiac impairments. Importantly, the cardiac injury was completely repaired as defined by normal cardiac functional and structural parameters. Since the now nearly 3 years old boy is
healthy, we were not allowed by the ethics board to perform GdMRI under general anesthesia, which however should be performed in the future to assay for possible remaining scar tissue.

Efficient heart regeneration is one of the prime visions for cardiology. Our report reveals that complete functional recovery of a massive myocardial infarction is possible in the newborn human. Thus, fundamental insights gained from cardiac regeneration in fish and neonatal mice might be indeed translatable to future cardiac repair in humans. Whether in humans functional cardiac recovery can also occur following permanent coronary vessel occlusion, as in the rodent MI models, or such recovery relies on reperfusion remains unresolved. Since cardiac repair in neonatal mice is limited to the first week after birth, we would like to urge the pediatric cardiologists to collect further cases of human infants to map the time window for cardiac functional recovery. In addition, it will be important to confirm our findings using imaging (e.g. MRI) of the damaged myocardium. Importantly, our report suggests that humans might have the intrinsic capacity to regenerate their hearts as was shown experimentally for other neonatal mammals. Due to the nature of our human case report we cannot exclude hibernation or stunning and cannot directly prove cellular cardiac regeneration. However, comparable adult human MIs following a proximal LAD occlusion for more than 24 hours with concurrent increases in cardiac enzymes would, based on clinical experience, not result in functional cardiac recovery. Our case report provides a crucial proof of concept on functional cardiac recovery in newborn humans that merits further basic and translational research to possibly one day be able to regenerate a diseased adult human heart.

ACKNOWLEDGMENTS
We thank all lab members for helpful discussions.

SOURCES OF FUNDING
J.M.P. is supported by grants from IMBA, the Austrian Ministry of Sciences, the Austrian Academy of Sciences, and an EU ERC Advanced Grant. We acknowledge funding from a Fondation Leducq Transatlantic Network of Excellence award.

DISCLOSURES
None.
REFERENCES

17. Flink IL. Cell cycle reentry of ventricular and atrial cardiomyocytes and cells within the epicardium following amputation of the ventricular apex in the axolotl, amblystoma mexicanum: Confocal microscopic immunofluorescent image analysis of bromodeoxyuridine-labeled nuclei. Anat Embryol (Berl). 2002;205:235-244

DOI: 10.1161/CIRCRESAHA.115.307017


25. White HD. Pathobiology of troponin elevations: Do elevations occur with myocardial ischemia as well as necrosis? J Am Coll Cardiol. 2011;57:2406-2408


FIGURE LEGENDS

Figure 1. Neonatal myocardial infarction. A, Electrocardiograms (ECG) of the newborn patient during the acute phase of myocardial infarction. Arrows indicate acute ischemic signs in the patient’s ECGs. The different time points show ECG changes typical for progressive myocardial infarction. X-axis = 50mm/s. Note that limb leads at 3 ½ hours (left panel) were originally recorded at 25mm/s. B, M-mode echocardiographic images of the patient’s heart in comparison to a healthy control on the first day of life. LVEDD = left ventricular enddiastolic diameter. LVESD = left ventricular endsystolic diameter. C,D, Time course analysis of serum troponin T (C) and creatine kinase (D) within the first 48 hours after birth. The green lines indicate the upper limit of healthy age-matched controls.

Figure 2. Thrombotic occlusion of the proximal left anterior descending artery (LAD). A, Doppler echocardiography of the patient’s LAD before and after thrombolysis. Data are from the day of birth (before thrombolysis) and three days later (after thrombolysis). B, Invasive coronary angiography confirmed a proximal thrombotic LAD occlusion leading to antero-septal myocardial infarction. Left panels show angiographic pictures of the target lesion (arrows) from two different imaging planes (upper panel = antero-posterior view, lower panel = lateral view). After initiation of thrombolysis, angiography proved re-opening of the coronary vessel (right panels). Data are from the day of birth (before thrombolysis) and three days later (after thrombolysis).

Figure 3. Severe ischemic myocardial damage. A, B-mode image of the patient’s left ventricle (right panel) after successful reperfusion therapy showed massive myocardial edema spanning from the septum to the anterior wall (yellow framed area and asterisks). Moreover, marked pericardial effusion was observed (#). A representative image from an age-matched healthy child is shown. LV = left ventricle. LA = left atrium. Data are from day 3 after birth. B, Supplementary videos demonstrating significantly impaired left ventricular function in the patient at day 3 after birth compared to a healthy control child. C, Electrocardiographic evaluation of the patient’s heart after reperfusion therapy showed pathologic Q-waves (arrows) indicative of persistent myocardial damage. Data are from the third day after birth. X-axis = 50mm/s.

Figure 4. Functional cardiac recovery. A-C, Time course of serum troponin T, creatine kinase (A), NTproBNP (B), and cardiac function as defined by fractional shortening and ejection fraction (C) in our patient. Green lines indicate the upper (troponin T, creatine kinase, NTproBNP) and lower (fractional shortening and ejection fraction) normal values in representative healthy age-matched children. D, Representative M-mode images from the patient’s heart at hospital discharge at day 51 after birth (right) in comparison to a healthy control (left panel). LVEDD = left ventricular enddiastolic diameter. LVESD = left ventricular endsystolic diameter.
Novelty and Significance

What Is Known?

- Adult mammalian hearts do not significantly regenerate irreversible damaged myocardium e.g. following myocardial infarction.

- Cardiac regeneration has been demonstrated in neonatal rodents following experimental apex resection and left anterior descending artery ligation.

What New Information Does This Article Contribute?

- Here, we report a rare human case of functional cardiac recovery following neonatal myocardial infarction. In the light of the recently established concept of mammalian neonatal cardiac regeneration in rodents, these data suggest potential similarities in the human heart.

Major efforts are underway to develop strategies for myocardial recovery. Complete cardiac regeneration has been demonstrated in fish and newborn mice following apex resection or cardiac infarctions. However, adult mammalian hearts do not significantly regenerate irreversible damaged myocardium. One key question is: Can one translate these experimental regeneration models in fish or neonatal mouse to humans considering fundamental differences in basic cardiac physiology? Here we report the case of severe myocardial infarction and cardiac damage in a newborn child on the first day of life. Remarkably, within weeks after the initial ischemic insult, we observed complete cardiac recovery, which translated into long-term normal heart functions. These data show that humans have the intrinsic capability to functionally repair myocardial damage. Whether the observed improvement is due to bona fide regeneration or reversible functional impairment remains unsolved.
Figure 3
Figure 4
Functional Recovery of a Human Neonatal Heart After Severe Myocardial Infarction
Bernhard J Haubner, Johanna Schneider, Ulrich U Schweigmann, Thomas Schuetz, Wolfgang Dichtl, Corinna Velik-Salchner, Joerg-Ingolf Stein and Josef M Penninger

Circ Res. published online December 9, 2015;
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/early/2015/12/09/CIRCRESAHA.115.307017

Data Supplement (unedited) at:
http://circres.ahajournals.org/content/suppl/2015/12/09/CIRCRESAHA.115.307017.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at: http://circres.ahajournals.org//subscriptions/
Supplemental Material

Detailed Methods

Electrocardiograms (ECG) were analyzed using standard 12-lead ECG equipment (CardioSoft V.6.71 GE Healthcare). Serum biomarkers were measured in the Central Institute for Medical and Chemical Laboratory Diagnostics, Innsbruck Medical University, Austria using a high sensitive assay for troponin T (ElektroChemiLumineszenz ImmunoAssay ECLIA-TnT, Roche Diagnostics GmbH Mannheim, Germany, normal range: 0-14ng/L) and standard assays for creatine kinase (CKCobas®c-test, Roche Diagnostics GmbH Mannheim, Germany, normal range: 39-190U/L) and NTproBNP (ElektroChemiLumineszenz ImmunoAssay ECLIA-ELICA NT-BNP, Roche Diagnostics GmbH Mannheim, Germany, normal range: 0-278ng/L). Echocardiographic images were acquired using Siemens Sequoia systems. Invasive angiography was performed using standard cardiac catheterization equipment from Siemens. Thrombolysis was initiated approximately 28 hours after birth using alteplase (0.1mg/kgBW; Actilyse, Boehringer Ingelheim, Vienna).
Online figure I. Timelines of clinical interventions during the patient’s first 48 hours after birth. A, Timeline of the patient’s clinical evaluation and therapy during the first 48 hours after birth. APGAR = Standardized score to assess the health of newborn children immediately after birth (appearance, pulse rate, reflex, activity, respiration are accounted; ranges from 0-10 and is measured at 1, 5, and 10 minutes after birth). LV = left ventricle. ECMO = extracorporeal membrane oxygenation. LAD = left anterior descending artery. ECG = electrocardiogram. ICU = intensive care unit. B, Time course analysis of NTproBNP within the first 2 days after birth. Green line indicates the upper normal limit.
Online figure II. Evaluation of the patient within the first year of life. A, Weight gain and growth of the patient during the first 30 months. B, C, Representative M-mode images (B) and B-mode videos (C) of the patient’s heart at the end of his first year of life in comparison to an age-matched healthy control. LVEDD = left ventricular enddiastolic diameter. LVESD = left ventricular endsystolic diameter.