Despite significant improvements in prevention and therapies, the burden of myocardial infarction (MI) remains high. 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

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 after 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 after myocardial infarction.

Methods and Results: Here, we report the case of a newborn child having 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. (Circ Res. 2016;118:216-221. DOI: 10.1161/CIRCRESAHA.115.307017.)

Key Words: angiography ■ cell death ■ heart failure ■ myocardial infarction ■ regeneration
Results
A 27-year-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 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, were massively increased within hours after birth (Figure 1C and 1D). Moreover, we detected increased levels of N-terminal pro B-type natriuretic peptide (Online Figure IB), a well-established marker of elevated intracardiac pressure. Of note, troponin T is released from dying cardiomyocytes and directly correlates with the extent of cardiomyocyte necrosis. In our patient, we found troponin T serum levels close to 15 000 ng/L (Figure 1C), levels that are even higher than in severe cases of MIs in the adult. Thus, all these parameters show that the newborn child had severe cardiac injury.

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Figure 1. Neonatal myocardial infarction. A, ECGs 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=50 mm/s. Note that limb leads at three and a half hours (left) were originally recorded at 25 mm/s. B, M-mode echocardiographic images of the patient’s heart in comparison with a healthy control on the first day of life. C and 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. LVEDD indicates left ventricular enddiastolic diameter; and LVESD, left ventricular endsystolic diameter.
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, for example, 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 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 and 2B). 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 and 3B; Online Movies I and II). Moreover, after thrombolysis, we detected pathological ECG Q waves (Figure 3C), further supporting myocardial damage. Thus, the newborn had LAD occlusion for >20 hours, resulting in massive MI.

The following subacute phase was characterized by continuous cardiac improvement without any complications. All serum markers for cardiac damage, that is, troponin T and creatine kinase, rapidly returned to normal levels (Figure 4A). Moreover, N-terminal pro B-type natriuretic peptide serum level returned to background levels (Figure 4B). In line with normalized N-terminal pro B-type natriuretic peptide levels, cardiac function, that is, fractional shortening and ejection fractions, markedly improved to levels observed in age-matched, healthy normal children (Figure 4C and 4D). 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 ≤1 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 1 year of age, echocardiography and N-terminal pro B-type natriuretic peptide evaluations showed normal cardiac morphologies and heart function (Figure 4B and 4C; 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.

**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 3 days later (after thrombolysis). **B**, Invasive coronary angiography confirmed a proximal thrombotic LAD occlusion leading to anteroseptal myocardial infarction. Left, Angiographic pictures of the target lesion (arrows) from 2 different imaging planes (top=anteroposterior view and bottom=lateral view). After initiation of thrombolysis, angiography proved reopening of the coronary vessel (right). Data are from the day of birth (before thrombolysis) and 3 days later (after thrombolysis).

**Figure 3.** Severe ischemic myocardial damage. **A**, B-mode image of the patient’s left ventricle (right) 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. Data are from day 3 after birth. **B**, Online Movies demonstrating significantly impaired left ventricular function in the patient at day 3 after birth compared with a healthy control child. **C**, Electrocardiographic evaluation of the patient’s heart after reperfusion therapy showed pathological Q waves (arrows) indicative of persistent myocardial damage. Data are from the third day after birth. x axis=50 mm/s. LA indicates left atrium; and LV, left ventricle.
Discussion

We present the case of a newborn patient with severe anteroseptal ST elevation MI, confirmed by multiple assays, such as angiography, ECG, echocardiography, and increased cardiac serum biomarkers. Amazingly, the patient’s heart rapidly recovered despite 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 having MI in the neonatal period without structural heart disease.26–32 All reported newborns with documented MI that survived the acute phase apparently recovered their heart function.26–28,31,32 Because 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.33 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 severe MI with subsequent severe structural and functional cardiac impairments. Importantly, the cardiac injury was completely repaired as defined by normal

Figure 4. Functional cardiac recovery. A–C, Time course of serum troponin T, creatine kinase (A), N-terminal pro B-type natriuretic peptide (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, and 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 with a healthy control (left). ECMO indicates extracorporeal membrane oxygenation; LVEDD, left ventricular enddiastolic diameter; and LVESD, left ventricular endsystolic diameter.
cardiac functional and structural parameters. Because the now nearly 3-year-old boy is healthy, we were not allowed by the ethics board to perform gadolinium-enhanced magnetic resonance imaging 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 MI 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 after permanent coronary vessel occlusion, as in the rodent MI models, or such recovery relies on reperfusion remains unresolved. Because 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 (eg, magnetic resonance imaging) 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. Because of 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 after a proximal LAD occlusion for >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 1 day be able to regenerate a diseased adult human heart.

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Disclosures

None.

References


**Novelty and Significance**

**What Is Known?**
- Adult mammalian hearts do not significantly regenerate irreversible damaged myocardium, for example, after myocardial infarction.
- Cardiac regeneration has been demonstrated in neonatal rodents after 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 after 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 after 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 because of bonafide regeneration or reversible functional impairment remains unsolved.
Functional Recovery of a Human Neonatal Heart After Severe Myocardial Infarction
Bernhard J. Haubner, Johanna Schneider, Ulrich Schweigmann, Thomas Schuetz, Wolfgang Dichtl, Corinna Velik-Salchner, Joerg-I. Stein and Josef M. Penninger

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Electrocardiograms (ECG) were analyzed using standard 12-lead ECG equipment (CardioSoft V6.71 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.