SUPPLEMENTAL MATERIAL
Expanded Methods

**Mouse models:** Cardiomyocyte-specific cyclin C-knockout mice: Cyclin C floxed mice (cyclin C fl/fl) were kindly provided by Dr. Peter Sicinski (Harvard University) and cyclin C cardiac-specific knockout (cKO) mice were generated by breeding cyclin Cfl/fl mice with C57/BL6 transgenic mice containing the α-myosin heavy chain (α-MHC) promoter-driven cre recombinase to establish heterozygous cyclin Cfl/+;αMHC-Cre mice. Male cyclin Cfl/+-αMHC Cre+ mice were bred to female cyclin C fl/fl mice to establish homozygous cyclin C fl/fl; αMHC Cre/+. Studies were done using Cre-negative cyclin C fl/fl littermates as controls.

Conditional cardiomyocyte-specific cyclin C-overexpressing mice were generated by the University of Iowa Genome Editing Facility by pronuclear injection of a linearized targeting vector into B6 × SJL F2 eggs. The targeting construct was made by replacing the ZsGreen coding sequence of pCAG-loxPSTOPloxP-ZsGreen (Addgene #51269) with the coding region of CCNC (NCBI accession NM_005190) containing a C-terminal Myc tag. Founders were identified by genotyping with primers specific for the hGH polyA sequence downstream of CCNC (forward, 5′-GTCTATTCCGGAACCAAGCTGGAGT-3′; reverse, 5′-AACAGGCATCTACTGAGTGGACCA-3′) and backcrossed to C57BL/6 mice (Charles River Laboratories, strain code 027) for at least 5 generations for all studies. Cyclin C overexpression was induced through crossing loxPSTOPloxP-CCNC mice with αMHC-Cre expressing mice. Unless otherwise stated, at least 3 transgenic (fl/+; Cre+) and 3 fl/+ littermate control mice were used for all experiments. Similar results were obtained between male and female animals. Age-matched cyclin C fl/+; Cre negative and Myh6-Cre alone were used as
controls. Animals were fed standard chow and water given ad libitum. All experimental procedures were approved by the University of Iowa Animal Care and Use Committee.

**Human explanted heart specimen procurement:** The human explanted heart samples were collected under the protocols approved by the Health Research Ethics Board of the University of Alberta. Signed consent and assent were obtained from individual participant (or next of kin) prior to cardiac transplantation or organ donation. Non-failing myocardial specimens were procured from n=5 consecutive donors with no cardiovascular history who were unsuitable for transplant due to medical or technical issues, such as ABO blood type incompatibility, as per Human Organ Procurement and Exchange Program at the University of Alberta Hospital. Adult failing heart tissues were collected from patients with end-stage heart failure secondary to ischemic coronary artery diseases (n=6) as part of the Human Explanted Heart Program at the Mazankowski Alberta Heart Institute. The collections were conducted when the patients underwent cardiac transplantations, and all myocardium samples were excised from the post-MI left ventricular free wall avoiding epicardial adipose tissue within 5-10 minutes of its excision following cold cardioplegia. The samples were immediately flash-frozen in liquid nitrogen and later stored in ultra-low (-80°C) freezers. Detailed demographic and clinical profile of all patients with coronary artery diseases are summarized in Table 1. The non-failing control group consisted of n=5 explanted hearts from males with a median age 52 years (IQR 38.0–54.0 years) and median LVEF of 60% (IQR 60-65%).

**Cell culture:** To isolate primary cultures of neonatal rat cardiomyocytes (NRCM), hearts from P3 Wistar rats (Jackson labs) were rapidly excised and washed in chilled Hanks Balanced Salt Solution (HBSS, 1X). The atria were removed and ventricles carefully minced and dissociated into single cells by proteolytic enzymes (Pierce Primary Cardiomyocyte Isolation Kit) dissolved
in HBSS in a 37°C incubator for 30-35 min with gentle stirring. Enzymes were removed and cells were washed 3 times with chilled HBSS. To breakup tissue, cells were gently pipetted repeatedly with L- Dulbecco’s modified Eagle’s medium DMEM (M199, 10% horse serum, 5% fetal bovine serum, 1% penicillin). Cells were plated onto collagen-coated culture plates and allowed to adhere to the plates for 24 hours before changing to basic experimental culture DMEM media (M199, 2% fetal bovine serum, 1% penicillin). NRCMs were stressed with Angiotensin II (100 nM, Sigma), Isoproteonol (200 nM, Sigma) or palmitate (50 μM, Sigma) 48 hours post seeding for varied durations. The culture medium was changed daily until the cells were harvested.

**Adeno-associated virus expression:** Primary NRCM were plated onto collagen-coated (BD Biosciences) coverslips and maintained in modified DMEM culture (Pierce Primary Cardiomyocyte Isolation DMEM cell culture) medium for 24 hours. Cells were infected with adeno-associated virus (5x10^7 vg/uL) containing cDNA for wild type cyclin C, mutant cyclin C-HAD, mutant cyclin C-ND, or GFP (empty vector control) for 72 hours. Adeno-associated vectors were generated by the University of Iowa Gene Vector Core Facility.

**Cellular and whole heart lysate fractionation:** Following treatment, cells were collected and fractionation was completed using the NE-PER Nuclear and Cytoplasmic Extraction kit (Thermo) according the manufacturer’s instructions. Cells and tissue were washed with chilled PBS and centrifuged at 500xg for 5 minutes. Supernatant was discarded; cytoplasmic and nuclear proteins were extracted and stored at -80°C degrees. Equal protein amounts from each fraction were analyzed by Western blotting.

**Quantitative real-time PCR (qRT-PCR):** Ventricular tissue was isolated and flash frozen in liquid nitrogen and stored at −80°C until processed. Flash frozen ventricles were pulverized with
a Bessman tissue pulverizer before homogenization. Total RNA was extracted in TRIzol reagent (Invitrogen) using a Postter-elvehjem tissue grinder. Reverse transcriptase-PCR was performed to generate cDNA using SuperScript-III (Invitrogen). For qRT-PCR, 50 ng of cDNA were used for each reaction with iTAQ Universal Sybergreen reagent (BioRad) using the QuantStudio 6 Flex system (Applied Biosystems). Gene expression was analyzed using the ΔΔCT method and relative expression was normalized to Rpl7l1. Sequences for the primers are as listed in previous studies.1, 2

**Immunofluorescence microscopy:** Isolated NRCMs were grown on collagen-coated glass coverslips. After treatment, cells were washed 3 times with PBS and fixed with ice cold ethanol (100% v/v) for 15 minutes at room temperature. To suppress unspecific labeling, cells were incubated with blocking solution (1% BSA, 1% goat serum, and 0.1% Triton X-100 in PBS) for 1 hour at room temperature. Rabbit anti-Cyclin C (1:100, Bethyl, Thermo) antibody, Mitotracker orange (1:500, Sigma) and Phallodin-647 (1:400, Life Technologies) in 1% BSA solution (in PBS, pH 7.4) were added for 1 hour at room temperature. After three washes with chilled PBS the secondary antibodies conjugated with Alexa Flour 488 or Alexa Flour 568 (1:300) were added for 1 hour at room temperature. Cells were washed and mounted with vecta shield (Vectorlabs) containing DAPI for nuclear staining. Immunofluorescence was observed using a Zeiss 710 confocal microscope. Whole hearts are harvested, paraffin-embedded, and cut into 10μm sections with a rotary microtome (Leica). Following dewaxing, rehydration and antigen retrieval, sections are incubated with blocking solution (0.1% TBS/T / 10% goat serum; 30 minutes at room temperature), followed by incubation with primary antibody (Ab°) either overnight at 4 °C or 1–2 hours at room temperature and secondary antibodies conjugated to either Alexa 488 or Alexa 594 (Life Technologies) for two hours at room temperature. Fluorescent
slides are washed, then mounted with Vectashield Mounting medium with DAPI (Vector Labs).

Immunofluorescence is observed using a Zeiss 710 confocal microscope.

**Immunohistochemical staining:** All samples were processed in consultation with the University of Iowa Central Microscopy Facility and Comparative Pathology core. Briefly, hearts were fixed in 4% paraformaldehyde, paraffin embedded and sectioned (10µm) using a standard microtome. Heart sectioned were deparaffinized and stained to determine changes in morphology (hematoxylin and eosin (H&E)) and fibrosis (Masson’s trichrome) as previously published1,2.

**Immunoblot analysis:** Isolated NRCM were removed from plates with 0.25% Trypsin in 37°C incubator for 3-5 min. Cells were washed twice with PBS and centrifuged at 30,000xg for 10 minutes. Whole hearts were harvested and rinsed with chilled PBS. Ventricles were flash frozen and kept at –80°C until processing for total protein. Ventricular tissue was pulverized with a Bessman tissue pulverizer (Spectrum Labs) and homogenized in RIPA buffer (25 mM Tris-HCl pH 7.6, 150 mM NaCl, 1% NP-40, 1% Na-deoxycholate, 0.1% SDS; Thermo Fisher Scientific) containing cOmplete Mini protease and phosphatase inhibitors (Roche). Cells or tissue samples were sonicated on ice for 10 seconds with an ultrasonic liquid processor (Qsonica) and centrifuged at 20,000 g at 4°C. Protein concentrations were determined by the bicinchoninic acid assay method (Thermo Fisher Scientific). Samples were separate for immunodetection using standard sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) using 20 µg lysate per lane was separated on 4%–20% Tris-glycine SDS gels (Bio-Rad Laboratories) and transferred to 0.45 µm polyvinyl difluoride membranes (EMD Millipore). Membranes were blocked in blocking buffer (10 mM Tris-HCl pH7.4, 150 mM NaCl, 0.05% Tween-20, 5% BSA or 5% nonfat dry milk), incubated in blocking buffer with primary antibodies overnight at 4°C, washed, and incubated with HRP-linked secondary antibodies (Jackson ImmunoResearch at
1:10,000) for 1 hour at room temperature. Primary antibodies were used at the following dilutions: Cyclin C (anti-rabbit, Bethyl, 1:2,000; Thermo, 1:1000), Drp1 (anti-rabbit, Cell Signaling, 1:500), pDrp1(616) (anti-rabbit, Cell Signaling (1:500), anti-rabbit, cytochrome C (Cell Signaling (1:1000). Gapdh (Cell Signaling 2118, 1:8,000), Topo-isomerase (Cell Signaling 1:500) and RNA-pol II (Sigma A7811, 1:10,000) were used as loading control.

**Mitochondria respiration analysis:** Complex activity was assessed using a Seahorse XF96 Extracellular Flux Analyzer by the University of Iowa Free Radical and Radiation Biology Research Core, following a protocol previously established\(^3\):\(^4\). NRCM’s were isolated and plated at 40,000 cells was loaded per well in the XF96 plate format and treated with Cyclin CAAV for 72 hours. Plates were spun at 4 °C at 2000 g for 20 minutes to affix cells to the wells. The assay was run in the presence of 5 mM pyruvate and 5 mM malate, with sequential injections of FCCP and Antimycin A to final concentrations of 4 μM apiece. A minimum of 7 technical replicates was used for each cell isolation and treatment. Statistical analysis was accomplished using Microsoft Excel.

The Oxygraph-2k (O2k, OROBOROS Instruments, Innsbruck, Austria) was used for measurements of respiration and combined with the Fluorescence-Sensor Green of the O2k-Fluo LED2-Module for H₂O₂ measurement at the University of Iowa Metabolic Core. Two O2k instruments were used in parallel. Experiments using tissue homogenate and permeabilized cells were performed in MiR05 (110 mM sucrose, 60 mM K-lactobionate, 0.5 mM EGTA, 3 mM MgCl₂, 20 mM taurine, 10 mM KH₂PO₄, 20 mM HEPES, pH 7.1 at 30 °C, and 0.1% BSA essentially fatty acid free). Dulbecco’s modified eagle medium supplemented with 10% fetal bovine serum and 50 units/mL penicillin and 50 μg/mL streptomycin was used for measurements.
on intact cells. All experiments were performed at 37 °C. The medium was reoxygenated when oxygen concentrations reached 80 µM.

**Myocardial infarction surgeries:** MI induction was performed as described\(^5\). Briefly, the mouse was placed in a supine position before intubation and ventilation as previously described using a rodent miniventilator (Harvard Apparatus, Hollston, MA) hooked up to an oxygen concentrator apparatus Millenium (Respironics, Marietta, GA) that provided 94–98% oxygen. The ventilator was set at positive end-expiratory pressure (PEEP) mode of ventilation with a stroke volume of 200 Al and at 200 strokes per minute. Surgery was performed using a Leica MZ 12 microscope. The left pectoralis major muscles were refracted towards the right shoulder and the left rectus thoracis and serratus anterior muscles were reflected towards the left with two hooked microretractors. The third intercostal space was exposed and delicately dissected 3 mm from the sterno–costal junction, avoiding injury to the left internal mammary artery. Thoracotomy proceeded laterally on the upper border of the fourth rib to avoid damaging the intercostal nerves and vessels on the lower border of the third rib. A 10/0 Prolene suture (Ethicon, Johnson & Johnson, Brussels, Belgium) was then passed under the LAD at 1 mm distal to left atrial appendage, immediately after the bifurcation of major left coronary artery. The chest wall was closed by approximating the third and fourth ribs with one or two interrupted stitch using a 5/0 Chromic Catgut absorbable suture (Ethicon, Johnson & Johnson, Brussels, Belgium). Skin closed with 6/0 Prolene continuous sutures. The mouse was gently disconnected from the ventilator and spontaneous breathing should resume almost immediately.

**Ischemic reperfusion surgeries:** Ischemia induction was performed as described\(^5\). Following 20 minutes of ischemia, the 10/0 prolene suture was removed to allow for reperfusion of the ischemic area and generation of I/R injury for 90 minutes. Next, the LAD was relegated and 2% Evans blue
was directly injected into aorta to observe ischemic and remote regions, which were immediately harvested. Throughout the process, similar intubation and ventilation processes were used as previously described for the MI procedure.

**Cardiac function analysis:** To identify potential changes in gross cardiac morphology and markers of heart failure, body weight (g), heart weight (ventricle and atria) and lung weight (mg) were measured. In order to determine and evaluate the degree of infarction, we used triphenyl tetrazolium chloride (TTC) staining on transverse heart sections. Sections will were incubated in 1% TTC in PBS for 20 min at 37 °C and fixed in 10% formalin overnight. The samples were imaged using a Leica MZ 12 dissection scope. Cardiac function was evaluated in conscious mice in the University of Iowa Cardiology animal phenotyping core laboratory. Left-sided chest hair was removed. Parasternal long and short axis views were obtained using a high-frequency echocardiography (30 MHz) linear array transducer (Vevo 2100; Visual Sonics). Measurements performed were done by a single experienced operator blinded to the mouse genotypes.

**RNA sequencing analysis:** The University of Iowa Institute of Human Genetics, Genomics Division, generated polyA-enriched stranded RNA libraries followed by RNAseq using the Illumina HiSeq platform. Raw sequence reads were analyzed with BaseSpace (www.illumina.com) by aligning reads to the Mus musculus mm10 genome using the TopHat Alignment app. Transcripts were assembled and significant differentially expressed genes were determined with the Cufflinks Assembly and DE app using a false discovery rate <0.05.

RNA-seq analysis list of differentially regulated genes significantly changed between cyclin C fl/fl and cyclin C cKO mouse hearts was entered into the PANTHER classification system (Pantherdb.org). Classification of data was compiled via Biological Process and a Pie Chart was created. Alterations in Biological Processes pertaining to Metabolic Processes was
performed to break down individual metabolic processes. RNA-seq analysis data was uploaded to Qiagen’s Ingenuity Pathway Analysis (IPA; Valencia, CA) and biological and interaction networks were generated. The gene list was analyzed for biological function enrichment analysis, upstream regulator analysis, and networks of interaction between molecules algorithmically generated based on their connectivity.

**High magnification transmission electron microscopy:** Jeol electron microscope (JEM-1230) was used at 1,500x-30,000x direct magnifications (Jeol) on 90-nm sections of fixed left ventricular tissue or AAR regions of sham or I/R treated hearts. All samples were processed in consultation with the University of Iowa Central Microscopy Facility. Tissue was fixed in 2% glutaraldehyde and 2% paraformaldehyde in 0.1M buffer, dehydrated and embedded in resin bead capsules and baked (70°C oven) for 24 hrs. Tissue was sectioned (0.9 µm thickness, Leica UC6 ultramicrotome II), on 300 µm mesh copper grids, stained using NaOH and lead citrate, and imaged. Mitochondrial size, area and length were measured using ImageJ in a double blind study. Analysis was performed using Matlab software. Briefly, mitochondrial length and area were binned, normalized to compute percentages and then plotted via histogram. Unbinned data was fit to a gamma distribution curve. Statistical analysis was performed using Kruskal Wallis to detect changes in distribution and a student T-test to detect changes in the mean.

**Pharmacological studies:** *In vitro* analysis: Isolated P3 NRCM was treated with the Cdk1 inhibitor, Roscovitine (R7772 SIGMA, MO): 5 µM, 6 hour treatment; NU6102 (CAS 444722-95-6, Sigma, MO): 5 µM, 6hour. *In vivo* analysis: Roscovitine (R7772 SIGMA MO) is solubilized in DMSO (Sigma, St. Louis, MO) and diluted in 0.9% sodium chloride. Intraperitoneal injection of Roscovitine was performed 1hour before ischemic reperfusion surgery.
**Coimmunoprecipitation (Co-IP):** The AAR region of ventricular lysates were harvested from 8-10 week old C57/bl-6 mice treated with sham or I/R surgeries and prepared using RIPA buffer with the addition of protease phosphatase inhibitor cocktail (Roche). Co-immunoprecipitation was performed using the Dynabead Protein A protocol (Thermo fisher, 10002D) and preformed according to manufacturer’s instructions. Briefly, Dynabeads were prepared and bound to 10 µg of Cdk1 (Santa cruz) or cyclin C antibody (Thermo) in 200 µL PBS with Tween-20, incubated for 20 minutes at room temperature. To the extracts, 5 µl of cyclin C (Thermo) or Cdk1(Santa cruz) antibody was added and incubated with gentle rotation for 2 hours at 4°C followed by the addition of 5 µl of Dynabeads Protein A (Invitrogen) with a further incubation of 1 to 2 hours. Immune complexes were washed, target antigen was eluted and gently resuspended in NuPAGE 4X LDS Sample Buffer (Thermo) and NuPAGE 10X Sample Reducing Agent (Thermo) and detected via immunoblotting in the presence of cyclin C(Thermo) or Cdk1 (Santa Cruz) antibodies.
Table S1. Baseline clinical characteristics of human explanted heart specimen.

| Demographic | Coronary Artery Diseases Median (IQR) |
|-------------|--------------------------------------|
| No. of Patients studied | 6 |
| Age at transplant (years) | 56.0 (47.8-60.5) |
| Sex (Male) | 6/6 |
| **Anthropometric** | |
| Weight (kg) | 85.0 (83.6-94.3) |
| Height (m) | 1.8 (1.7-1.8) |
| BMI (kg/m²) | 28.2 (25.3-32.1) |
| **Physical assessment** | |
| HR (bpm) | 83.0 (77.0-100.0) |
| SBP (mmHg) | 116.0 (95.5-142.5) |
| DBP (mmHg) | 70.0 (67.0-70.8) |
| NYHA (Class I/II/III/IV) | 0/0/0/6 |
| **Comorbidities (%)** | |
| COPD/Asthma | 1/6 |
| DM | 1/6 |
| Dyslipidemia | 2/6 |
| Kidney disease | 2/6 |
| HTN | 2/6 |
| Obesity | 4/6 |
| Other diseases | 4/6 |
| **History** | |
| Smoking | 4/6 |
| Alcoholic | 0/6 |
| **Echocardiography** | |
| LVEF (%) | 20.1 (17.5-22.7) |
| LVEDD (mm) | 55.5 (53.5-58.8) |
| LVESD (mm) | 39.0 (34.5-51.0) |
| **Blood Parameters** | |
| Hemoglobin (g/L) | 112.0 (93.5-135.0) |
| WBC (10⁹/L) | 7.8 (6.3-9.1) |
| BNP (pg/ml) | 973.0 (747.5-986.5) |
| Creatinine (μmole/L) | 97.5 (84.3-110.8) |
| eGFR (ml/min/1.73m²) | 71.5 (63.5-95.3) |
| **Devices** | |
| Pacemaker | 1/6 |
| ICD | 1/6 |
| BiV-ICD | 1/6 |
| VAD | 4/6 |
| **Medications** | |
| Medication          | Data   |
|--------------------|--------|
| ACEi/ARB           | 4/6    |
| Beta Blocker       | 3/6    |
| Diuretics          | 4/6    |
| Anti-coagulation   | 3/6    |
| Statin             | 3/6    |
| PPI                | 2/6    |
| Anti-arrhythmic    | 2/6    |
| Vitamin D          | 1/6    |

BMI = body mass index; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; NYHA = New York Heart Association; COPD = chronic obstructive pulmonary disease; LVEF = LV ejection fraction; LVEDD = LV end diastolic diameter; LVESD = LV end systolic diameter; WBC = white blood cell; eGFR = estimated GFR based on the MDRD equation; ICD = implantable cardioverter-defibrillator; BiV-ICD = biventricular implantable cardioverter-defibrillators; VAD = ventricular assist device; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; PPI = proton pump inhibitor. Available data are presented as medians (with lower and upper quartiles) or numbers, where appropriate.
Figure S1. Developmental cyclin C expression, cyclin C cTg histology and MI pathology data.
(A) Immunoblotting of cyclin C and Ponceau S protein stain in mouse heart tissues from time periods embryonic day (E) 18.5, postnatal day (P) 3, P7, P14, P21, 3 month, 6 month. (B) Representative heart sections of 12-wk old cyclin C cTg and fl/fl control mice stained with Masson’s trichrome and hematoxylin and eosin (H&E) for morphological and fibrotic analysis. (C) Histological images of paraffin embedded samples stained using (H&E) and Masson’s trichrome in 12-wk old Cyclin C cTg and fl/+ controls. (D) Gross hearts stained with Evans blue dye of 8 wk-C57/bl6 mice following 48hr sham or myocardial surgery. (E) Heart sections stained with 1.5% 2,3,5 triphenyltetrazolium chloride (TTC) of 8 wk-C57/bl6 mice following 48hr sham or myocardial surgery. (F) Heart weight to body weight ratios, ventricular mass, heart rate and end diastolic volume for cyclin C cTg and fl/+ controls. (G) Cumulative mitochondrial area distribution from cyclin C cTg and fl/+ controls with or without MI.
Figure S2. Ablation of cardiac cyclin C results in increased heart and lung mass and altered gene expression.
(A) Whole heart, body, and lung weights of 20-wk old cyclin C cKO and fl/fl controls. Data are means ± SE (n=6-10), **P < 0.05. (B) Representative heart sections and histological images of paraffin-embedded 12-wk old cyclin C cKO and fl/fl control mice stained with Masson’s trichrome and hematoxylin and eosin (H&E) for morphological and fibrotic analysis. Scale bars: 0.5mm. (D-E) mRNA expression of (c) Cdk8 and markers of cardiac failure (Nppb, Acta1, Actb, Myh6, and Myh7), (d) cardiac-specific genes (Tnni1, Tnni3), and (e) genes involved in metabolism (Ndufb7, Sdhb, Cox5a, Atp5g1) in ventricular tissue from 6-wk old cyclin C cKO and control hearts. (F) Enriched transcription factor binding motifs identified in the promoters of >1.5-fold upregulated (red) and >1.5-fold downregulated (blue) differentially expressed genes from RNA-seq results using WebGestalt tool.
Figure S3. Adult cardiomyocyte mitochondrial morphology is sensitive to stress and dependent on cyclin C and Cdk1.
(A) Immunofluorescence (IF) analysis of cyclin C (green) and α-actinin (red) in cardiomyocytes isolated from 8-wk old adult rats with and without palmitate treatment (50 µM, 30 min). (B-C) Mitochondrial number (c), form factor (d) and overall morphology (e) of NRCMs 72 hours after transduction with indicated AAV’s using Image J processing program. (**P<0.05; # = P<0.05; ANOVA, n> 400 cells counted, N=5). In (D), cells were treated with the Cdk1 inhibitor, NU6102 (5µM, 1hr) prior to staining nuclei with DAPI (blue) and mitochondria (red) with Mitotracker orange (200 nM).
Supplemental References:

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