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Methods to Induce Cardiac Hypertrophy and Insufficiency

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Animal models of cardiac hypertrophy and insufficiency have been reviewed by Hasenfuss (1988), Muders and Elsner (2000), Vanoli et al. (2004), Patten and Hall-Porter (2009), Dubi and Arbel (2010), Gomes et al. (2013), and Szymanski et al. (2012).

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Cardiac Hypertrophy and Insufficiency in Rats

Aortic Banding in Rats

Purpose and Rationale

Blood flow restriction of the aorta in rats induces not only hypertension but also cardiac hypertrophy within several weeks. Angiotensin-converting enzyme inhibitors, even at subantihypertensive doses, but not other antihypertensive drugs, inhibit cardiac hypertrophy (Linz et al. 1991, 1992a, 1996; Schölkens et al. 1991; Gohlke et al. 1992; Bruckschlegel et al. 1995; Ogawa et al. 1998).

Procedure

Male Sprague Dawley rats weighing 270–280 g are fasted 12 h before surgery. Anesthesia is induced by i.p. injection of 200 mg/kg hexobarbital. The abdomen is shaved, moistened with a disinfectant, and opened by a cut parallel to the linea alba. The intestine is moistened with saline and placed in a plastic cover to prevent desiccation. The aorta is prepared free from connective tissue above the left renal artery and underlaid with a silk thread. Then, a cannula no. 1 (0.9 × 40 mm) is placed longitudinally to the aorta

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and both aorta and cannula are tied. The cannula is removed, leaving the aortic lumen determined by the diameter of the cannula. The intestine is placed back into the abdominal cavity with the application of 5.0 mg rolitetracycline (Reverin). In sham-operated controls, no banding is performed. The skin is closed by clipping.

The animals are treated once daily over a period of 6 weeks with doses of the ACE inhibitor or other antihypertensive drugs found previously effective to lower blood pressure in rats. At the end of the experiment, blood pressure is measured under hexobarbital anesthesia (200 mg/kg i.p.) via indwelling catheters in the left carotid artery. Blood pressure measurement in conscious rats with the conventional tail-cuff method is not possible due to the large pressure difference across the ligature. Therefore, only one measurement at the end of the study is possible. The hearts are removed, rinsed in saline until free of blood, and gently blotted to dryness. Total cardiac mass is determined by weighing on an electronic balance to the nearest 0.1 mg. The atria and all adjacent tissues are trimmed off, and the weight of the left ventricle including the septum as well as the remaining cardiac tissue representing the right ventricle is determined separately. Weights are calculated per 100 g body weight.

Evaluation

The total cardiac mass and weight of left and right ventricle of treated rats are compared with operated controls and sham-operated controls.

Modifications of the Method

Uetmasu et al. (1989) described a simple method for producing graded aortic insufficiencies in rats and subsequent development of cardiac hypertrophy. Selective perforation of the right cup of the aortic valve or in combination with that of the left valve cup was performed using a plastic rod inserted from the right common carotid artery. Hypertrophy of the heart, but no hypertension or cardiac insufficiency, was observed.

Similar methods were used by Yamazaki et al. (1989) to study the alterations of cardiac adrenoceptors and calcium channels subsequent to aortic insufficiency, by Umemura et al. (1992) to study baroreflex and *β*-adrenoceptor function, and by Ishiye et al. (1995) to study the effects of an angiotensin II antagonist on the development of cardiac hypertrophy due to volume overload.

Hyperplastic growth response of vascular smooth muscle cells in the thoracic aorta was found following induction of acute hypertension in rats by aortic coarctation by Owens and Reidy (1985). Changes in cardiac gene expression during compensated hypertrophy and the transition to cardiac decompensation in rats with aortic banding were studied by Feldman et al. (1993). Muders et al. (1995) produced aortic stenosis in rats by placing a silver clip (inner diameter 0.6 mm) on the ascending aorta. Schunkert et al. (1995) studied alteration of growth responses in established cardiac pressure-overload hypertrophy in rats with aortic banding.

Prevention of cardiac hypertrophy after aortic banding by ACE inhibitors probably mediated by bradykinin could be shown (Linz et al. 1989, 1992a, b, 1993, 1994; Linz and Schölkens 1992; Schölkens et al. 1991; Weinberg et al. 1994).

Weinberg et al. (1997) studied the effect of angiotensin AT1 receptor inhibition on hypertrophic remodeling and ACE expression in rats with pressure-overload hypertrophy due to ascending aortic stenosis. Molina et al. (2009) described a novel experimental model of pressure-overload hypertrophy in young Sprague Dawley rats (200–250) created by placing a small titanium clip (internal diameter – 0.6 mm) in the aorta proximal to the right brachiocephalic artery. A decrease of 25 % in FS was observed 24–28 weeks after aortic constriction. Increased expression of β-myosin heavy chain, atrial natriuretic peptide, interleukin-1, interleukin-6, and TNF-α was also reported.

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Chronic Heart Failure in Rats

Purpose and Rationale

Rat models of heart failure were reviewed by Muders and Elsner (2000). Chronic heart failure can be induced in rats by occlusion of coronary arteries. One of the first reports was by Selye et al. (1960). More recent reports are by Pfeffer et al. (1979), Hodsman et al. (1988), Van Veldhuisen et al. (1994, 1995), Kajstura et al. (1994), Gómez et al. (1997), Liu et al. (1997a, b), and Jadavo et al. (2005).

Itter et al. (2004) described a model of chronic heart failure (CHF) in spontaneously hypertensive rats.

Procedure

Study Design Adult male 4-month-old SHR/NHsd and WKY/NHsd rats (Harlan Sprague Dawley, Winkelmann, Germany) weighing 250–300 g were used. Cardiovascular failure was induced by permanent (8 weeks) occlusion of the left coronary artery 2 mm distal to the origin from the aorta resulting in a large infarction of the free left ventricular wall.

Eight weeks after surgery, parameters indicating CHF were measured. Cardiac hypertrophy, function, and geometric properties were determined by the "working heart" mode and in vivo determinations by MRI and heart weight. Hydroxyproline/proline ratio was measured as an indicator of heart fibrosis.

Surgery The rats were anesthetized with a mixture of ketamine/xylazine (35/2 mg/kg) i.p. The left ventrolateral thorax was shaved and prepared to create a disinfected surgical access area. When a stable anesthesia was achieved, the animals were placed on a small animal operation table, intubated, and ventilated with room air using a small animal ventilator (KTR-4, Hugo Sachs Elektronik, March-Hugstetten, Germany). The level of anesthesia was deemed as adequate following loss of the pedal withdrawal reflex and absence of the palpebral reflex. The tidal volume was adjusted at 3–5 ml and the ventilation rate was 40 breaths/min. Left thoracotomy was performed via the third intercostal space. The heart was exposed and the pericardium opened. The left main coronary artery was ligated with Perma-Hand silk 4–0 USP (Ethicon, Norderstedt, Germany) near its origin at the aorta (2 mm distal to the edge of the left atrium). Ligation resulted in infarction of the free left ventricular wall. Ligation was deemed successful when the anterior wall of the left ventricle turned pale. At this point, the lungs were hyperinflated by increasing the positive end-expiratory pressure, and the chest was closed. The rats were placed on a heating pad. They were continuously monitored until they start moving in their cages. To

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avoid ventricular arrhythmias, lidocaine (2 mg/kg i.m.) was given before surgery. The sham procedure consisted of opening the pericardium and placing a superficial suture in the epicardium of the LV. To prevent acute lung edema, the rats received furosemide 2 mg/kg twice daily for 3 days via the drinking water.

Measurements at the End of the Study Before killing the animals 8 weeks after MI, noninvasive sequential nuclear magnetic resonance (NMR) measurements of heart geometric properties were done. Thereafter the animals were anesthetized with pentobarbitone (180 mg/kg i.p.) and subsequently heparinized (heparin sodium 500 IU/100 g body weight i.p.). Once stable anesthesia was achieved (stage III 3, reflexes absent), the animals were connected to an artificial respirator via a PE tube inserted into the trachea and ventilated with room air. The right carotid artery was cannulated with a polyethylene catheter to monitor mean blood pressure, systolic blood pressure, diastolic blood pressure, and heart rate over a stable time course of 10 min.

A transverse laparotomy and a right anterolateral thoracotomy were performed, and the heart was rapidly removed for the evaluation of its function in the working heart mode. Thereafter the heart weight, and the left and right ventricular weights were determined. For infarct size determination, the left ventricle was sectioned transversely into four slices from the apex to the base. The infarct size was determined by planimetry and expressed as a percentage of LV mass. Lung weight and further lung histology sections were evaluated. Hydroxyproline/proline ratio was determined in paraffin-embedded slices of the left ventricle.

Magnetic Resonance Imaging The animals were monitored by MRI at day 7 and day 42 post-MI. The rats were anesthetized with a mixture of 1 % halothane and 30/70 N_2O/oxygen with a specially manufactured rat mask. The fully anesthetized rats (phase III) were placed on a cradle made of Plexiglas in a supine position. Respiration and ECG were monitored continuously. MRI experiments were performed according to Rudin et al. (1991). The images were acquired by a spin-echo sequence SE (500/20), the field of view was 50 mm, and the image resolution was 256 $\times$ 256 pixels with a dimension of 0.2 $\times$ 0.2 mm. Four adjacent transverse slices were recorded; slice thickness was 1.5 mm. Before the acquisition of data, a coronary pilot scan was measured for adequate positioning of the transverse slices. MRI data acquisition was gated to the cardiac cycle by a Physiograd SM 785 MR monitoring system (Bruker, Karlsruhe, Germany). Two sets of transverse images were acquired, one at end-systole and another at end-diastole. End-diastole was defined as the image obtained 8 ms after the onset of the R wave of the ECG, corresponding to the largest cavity area. End-systole was defined as the image with the smallest LV cavity area. The image analysis was done using Bruker software (Karlsruhe, Germany). The parameters of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), septum size, infarct size, ejection fraction (EF), left ventricular chamber diameter (r), and circumference were measured. EF was estimated in percentage terms by the subtraction of LVESV from LVEDV. After the procedure, the rats were ventilated with oxygen, the mask was replaced, and they were brought back into their cages. They were monitored until they started moving in the cage.

Blood Pressure/Heart Rate The animals were anesthetized with pentobarbitone (180 mg/kg i.p.) and subsequently heparinized (heparin sodium 500 IU/100 g body weight i.p.). Once stable anesthesia was achieved, the animals were connected to an artificial respirator via a PE tube inserted into the trachea and ventilated with room air. The right carotid artery was cannulated with a polyethylene catheter. The catheter was connected to a PLUGSYS measuring system (Hugo Sachs Elektronik, March-Hugstetten, Germany) to monitor mean blood pressure, systolic blood pressure, diastolic blood pressure, and heart rate over a stable time course of 10 min.

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Working Heart For the final investigations, the heart of the anesthetized rat was rapidly removed and immersed in physiological buffer chilled to 4 °C. The aorta was dissected free and mounted onto a cannula (internal diameter: 1.4 mm) attached to a perfusion apparatus. The hearts were perfused according to the method of Langendorff with an oxygenated (95 % O_2/5 % CO_2) noncirculating Krebs–Henseleit solution of the following compositions (mM): NaCl, 118; KCl, 4.7; $CaCl_2$, 2.52; $MgSO_4$, 1.64; $NaHCO_3$, 24.88; KH_2PO_4, 1.18; glucose, 5.55; and Na-pyruvate, 2.0 at a perfusion pressure of 60 mmHg. Any connective tissue, thymus, or lung was carefully removed. A catheter placed into the pulmonary artery drained the coronary effluent perfusate that was collected for the determination of coronary flow and venous pO_2 measurements. The left atrium was cannulated via an incision of the left auricle. All pulmonary veins were ligated close to the surface of the atria. When a tight seal with no leaks had been established and after a 15-min equilibration period, the hearts were switched into the working mode, using a filling pressure (preload) of 12 mmHg in WKY/NHsd and 18 mmHg in SH rats. The afterload pressure was 60 mmHg in WKY/NHsd and 80 mmHg in SH rats. After validation of the basis parameters, the afterload pressure was enhanced in a cumulative manner from an additional 20–140 mmHg. Thereafter, the isovolumetric maxima were determined by enhancing the preload pressure in steps of 5–30 mmHg. Flow and pressure signals for computation were obtained from the PLUGSYS measuring system. Computation of data was performed with a sampling rate of 500 Hz, averaged every 2 s, using the software Aquire Plus V1.21f (PO-NE-MAH, Hugo Sachs Elektronik, March-Hugstetten, Germany).

Determination of Infarct Size After the evaluation of the external heart work, the total heart weight and the left and right ventricular weights were determined. The left ventricle was then sectioned transversely into four slices from the apex to the base. Eight pictures were taken of each rat heart, two from each slice. Total infarct size was determined by planimetry of the projected and magnified slices.

The area of infarcted tissue as well as the intact myocardium of each slice were added together and averaged. The infarcted fraction of the left ventricle was calculated from these measurements and expressed as a percentage of the LV mass. The left ventricular perimeter, diameter, infarct scar length, as well as wall thickness and infarct wall thinning were determined as well. According to Pfeffer et al. (1985) and Pfeffer and Pfeffer (1987), rats with infarct sizes <20 % and >40 % were excluded from the study.

Lung Histological Determination After lung weight determination, the organ was immersed in 4 % formalin (pH 7.0–7.5; 0.1 M). The lung was cut into small pieces, dehydrated, and embedded in paraffin. Hematoxylin and eosin (HE) sections were evaluated by light microscopy.

Hydroxyproline/Proline Ratio After embedding, the rest of the fixed left ventricular tissue was freeze-dried. Proline and hydroxyproline was then analyzed according to the method of López de León and Rojkind (1985) and the ratio of both were calculated.

Evaluation

The data are given as mean ± SEM. Statistics were performed using the SAS system statistics package (SAS Institute, Cary, N.C., USA) with a sequential rejection *t*-test.

Modifications of the Method

Jain et al. (2000) studied the effects of angiotensin II receptor blockade after coronary ligation and exercise training on treadmill in rats.

Medvedev and Gorodetskaya (1993) induced heart failure in rats by microembolization of coronary vessels with 15-μm plastic microspheres.

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Katona et al. (2004) found that selective sensory denervation by capsaicin aggravates adriamycin-induced cardiomyopathy in rats.

A simple and rapid method of developing high output heart failure and cardiac hypertrophy in rats by producing **aortocaval shunts** was described by Garcia and Diebold (1990). Rats weighing 180–200 g were anesthetized with 30 mg/kg i.p. pentobarbitone. The vena cava and the abdominal aorta were exposed by opening the abdominal cavity via a midline incision. The aorta was punctured at the union of the segment two-thirds caudal to the renal artery and one-third cephalic to the aortic bifurcation with an 18-gauge disposable needle. The needle was advanced into the aorta, perforating its adjacent wall and penetrating in the vena cava. A bulldog vascular clamp was placed across the aorta caudal to the left renal artery. Once the aorta was clamped, the needle was fully withdrawn, and a drop of cyanoacrylate glue was used to seal the aorta-punctured point. The clamp was removed 30 s later. The patency of the shunt was verified visually by swelling vena cava and the mixing of arterial and venous blood. The peritoneal cavity was closed with silk thread stitches and the skin with metallic clips. Rats with aortocaval shunts developed cardiac hypertrophy with significantly higher absolute and relative heart weights.

Other studies with aortocaval shunts in rats were published by Flaim et al. (1979) and Liu et al. (1991).

Isoyama et al. (1988) studied myocardial hypertrophy after creating aortic insufficiency in rats.

Terlink et al. (1998) studied ventricular dysfunction in rats with diffuse isoproterenol-induced myocardial necrosis.

Studies (Inoko et al. 1994; Klotz et al. 2006) have shown that Dahl-salt-sensitive rats when placed on a high-salt diet from the 6th week of age will develop concentric LV hypertrophy without chamber dilation around the 11th week and decompensate heart failure between the 15th and the 20th week. Introduction of the high-salt diet at 7 or 8 weeks of age will result in diastolic heart failure or systolic heart failure phenotypes, respectively (Doi et al. 2000).

Another rat model of systemic hypertension inducing heart failure is created by clipping one renal artery while leaving the contralateral kidney untouched. This induces systemic hypertension and LV concentric remodeling within 8 weeks (Junhong et al. 2008; Rizzi et al. 2010). Extensive LV fibrosis and diastolic dysfunction was also reported (Junhong et al. 2008).

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Cardiac Hypertrophy and Insufficiency in Mice

Cardiac Hypertrophy in Mice

Purpose and Rationale

Rockman et al. (1991, 1993) developed a model of ventricular hypertrophy in the intact mouse by use of microsurgical techniques.

Procedure

Eight-week-old adult mice weighing 18–22 g are anesthetized by intraperitoneal injection of a mixture of 100 mg/kg ketamine, 5 mg/kg xylazine, and 2.5 mg/kg morphine. Animals are placed under a dissecting microscope in the supine position, and a midline cervical incision is made to expose the trachea and carotid arteries. After endotracheal intubation, the cannula is connected to a volume-cycled rodent ventilator on supplemental oxygen with a tidal volume of 0.2 ml and a respiratory rate of 110 per min. Both left and right carotid arteries are cannulated with flame-stretched PE50 tubing. Catheters are connected to modified P50 Statham transducers.

The chest cavity is entered in the second intercostal space at the left upper sternal border through a small incision, and the thymus is gently deflected out of the field of view to expose the aortic arch. After the transverse aorta is isolated between the carotid arteries, it is constricted by a 7.0 nylon suture ligature against a 27-gauge needle, the latter being promptly removed to yield a constriction of 0.4-mm diameter and provide a reproducible transverse aortic constriction of 65–75 %.

The hemodynamic effects of acute and chronic constriction are followed by monitoring the pressure gradient between the two carotid arteries in anesthetized animals. Systolic and mean arterial pressure at baseline, during total occlusion when the ligature is tied, and early (15 min) and late (7 days) after transverse aortic constriction are recorded. The increase in systolic pressure provides an adequate mechanical stimulus for the development of cardial hypertrophy.

To confirm myocardial hypertrophy, both sham-operated and aortic-constricted hearts are examined 7 days after operation. Hearts examined for *cell size* are perfused with 4 % paraformaldehyde/1 % glutaraldehyde through the apex, immersed in osmium tetroxide, dehydrated in graded alcohols, and embedded in araldite. Tissue blocks are sectioned at a thickness of 1 μm, mounted on slides, and stained with toluidine blue. Cell areas are measured by manually tracing the cell outline on an imaging system connected to a computer.

At the end of the experiment, mice were sacrificed in anesthesia, heart excised, and weighed, the atria and ventricles separately frozen in liquid nitrogen for Northern blot analysis. Total RNA is extracted by a

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single-step extraction with guanidinium thiocyanate. The RNA is size fractionated by agarose gel electrophoresis, transferred to nylon membranes by vacuum blotting, and hybridized with the appropriate complementary DNA probes labeled with ^{32}P by random priming to a specific activity of $0.95–1.2 \times 10^6$ cpm/ng.

Evaluation

Variables measured are expressed as mean ± SD. Statistical significance of differences between sham-operated and thoracic aortic-constricted animals is assessed by Student's *t*-test.

Modifications of the Method

Dom et al. (1994) studied myosin heavy chain regulation and myocytes' contractile depression after LV hypertrophy in aortic-banded mice.

Okada et al. (2004) subjected mice to transverse aortic constriction. Echocardiographic analysis demonstrated cardiac hypertrophy and failure 1 and 4 weeks after surgery. Cardiac expression of endoplasmatic reticulum chaperones was significantly increased, indicating that pressure overload by transverse aortic constriction induced prolonged endoplasmatic reticulum stress.

Stansfield et al. (2007) described a minimally invasive murine model of transverse aortic constriction debanding, in which the band is removed up to 4 weeks after constriction through the same suprasternal incision. This reversible model of pressure overload was shown as an interesting model to study the molecular mechanisms involved in LV reverse remodeling.

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Chronic Heart Failure in Mice

Purpose and Rationale

Several authors reported the development of murine models of cardiac failure (Kaplan et al. 1994; Rockman et al. 1994; Balasubramaniam et al. 2004; Suzuki et al. 2004; Walther et al. 2004; Wang et al. 2004; Liao et al. 2005).

Xu et al. (2004) studied cardioprotection in mice with heart failure by dual inhibition of angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP).

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Procedure

Mice with a targeted deletion of the B_2 kinin receptor gene or C57BL/6 J mice at an age of 10–12 weeks were anesthetized with 50 mg/kg sodium pentobarbital i.p., intubated and ventilated with room air using a positive-pressure respirator. A left thoracotomy was performed via the fourth intercostal space; the lungs were retracted to expose the heart, and the pericardium was opened. The left anterior descending coronary artery was ligated with an 8–0 nylon suture near its origin between the pulmonary outflow tract and the edge of the left atrium. Acute myocardial ischemia was considered successful when the anterior wall of the left ventricle turned pale and an obvious ST segment elevation was observed. The lungs were inflated by increasing positive end-expiratory pressure and the thoracotomy site was closed. Sham-operated mice were subjected to the same procedure except that the suture around the left anterior coronary artery was not tied. Systolic blood pressure was measured in conscious mice using a noninvasive computerized tail-cuff system. Cardiac geometry and function were evaluated with a Doppler echocardiographic system. LV diastolic dimension was measured and ejection fraction was calculated from

$$\left[\frac{(\mathrm{LVAd} - \mathrm{LVAs})}{\mathrm{LVAd}}\right] \times 100,$$

where LVAd is the LV diastolic area and LVAs is the LV systolic area.

Four weeks after surgery, each strain was separated into one group treated with an ACE inhibitor, one group treated with a NEP inhibitor, one group treated with both inhibitors, and one control group. All drugs were administered in drinking water for 20 weeks.

At the end of the study, all mice were anesthetized with pentobarbital and the heart stopped at diastole by intraventricular injection of 15 % KCl. The heart, lungs, and liver were weighed to assess hypertrophy and congestion. Infarct size was determined by Gomori trichrome staining and expressed as the ration of the infarcted portion to total LV circumference.

Sections (6 μm) from each slice were double stained with fluorescein-labeled peanut agglutinin to delineate the myocyte cross-sectional area and interstitial space and rhodamine-labeled *Griffonia simplicifolia* lectin I to show the capillaries. To calculate interstitial collagen fraction, the total surface area (microscopic field), interstitial space (collagen plus capillaries), and area occupied by capillaries alone were measured by computer-assisted videodensometry.

After 20 weeks of treatment, plasma renin was measured.

Evaluation

Data were expressed as mean ± SE. Mortality rates were compared using χ^2 tests. For the echo, blood pressure, heart weight, lung weight, infarct size, plasma renin concentration, and histology data, paired or two-sample tests using nonparametric methods were used to perform all comparisons of interest.

Modifications of the Method

Scheuermann-Freestone et al. (2001) established a new mouse model of chronic volume overload by an aortocaval shunt. Congestive heart failure was induced, which resulted in the development of myocardial hypertrophy, impaired cardiac function, and increased expression of the natriuretic peptides in the left ventricle.

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Transgenic Mice and Heart Failure

Purpose and Rationale

Several hundreds of papers on transgenic mice and heart failure are published. Only a few can be mentioned here.

Chien (1995) described cardiac muscle diseases in genetically engineered mice.

Edwards et al. (1996) described severe cardiomyopathy in transgenic mice overexpressing the skeletal muscle myogenic regulator *myf5*.

Arber et al. (1997) found that MLP-deficient mice exhibit a disruption of cardiac cytoarchitectural organization, dilated cardiomyopathy, and heart failure.

Graham et al. (1997) described a mouse model for mitochondrial myopathy and cardiomyopathy resulting from a deficiency in the heart/muscle isoforms of the adenine nucleotide translocator.

Iwase et al. (1997) studied cardiomyopathy in transgenic mice induced by overexpression of the cardiac stimulatory G protein α-subunit.

Knollmannn et al. (2000) reported remodeling of ionic currents in hypertrophied and failing hearts of transgenic mice overexpressing calsequestrin.

Beggah et al. (2002) described reversible cardiac fibrosis and heart failure induced by conditional expression of an antisense mRNA of the mineralocorticoid receptor in cardiomyocytes.

Verheule et al. (2004) found increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of TGF-β1.

Duncan et al. (2005) found that chronic xanthine oxidase inhibition prevents myofibrillar protein oxidation and preserves cardiac function in a transgenic mouse model of cardiomyopathy.

Hartil and Charron (2005) reviewed mouse models where transgenic technology has been utilized to alter expression of genes involved in cardiac uptake and metabolism of either lipid or carbohydrate.

Hilfiker-Kleiner et al. (2005) reported that STAT3 knockout mice harboring a cardiomyocyte-restricted deletion of STAT3 showed enhanced susceptibility to cardiac injury caused by myocardial ischemia, systemic inflammation, or drug toxicity.

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Sanbe et al. (2005) studied reversal of amyloid-induced heart disease in desmin-related cardiomyopathy.

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Cardiac Insufficiency in Guinea Pigs

Purpose and Rationale

Congestive heart failure in man is characterized by cardiac hypertrophy, peripheral edema, lung and liver congestion, dyspnea, hydrothorax, and ascites. Effective treatment is achieved by cardiac glycosides. Based on techniques reported by Selye et al. (1960), a method was developed to induce congestive heart failure in guinea pigs with symptoms very close to human pathology (Vogel and Marx 1964; Vogel et al. 1965).

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Procedure

Male guinea pigs weighing 250–400 g are used. The fur at the ventral thorax is shaved and the skin disinfected. The animal is anesthetized with ether. The skin is cut with scissors on the left side at a length of 4 cm. The left musculus pectoralis is cut at the costal insertion and elevated. The forth intercostal space is opened with two blunted forceps. The heart is pressed against the opening with the left hand. The pericardium is opened with a fine forceps and pulled back to the basis of the heart. The beating heart is extruded from the thorax wound by pressure with the left hand on the right thorax wall. A ring-shaped clamp covered with a thin rubber tube is placed around the basis of the heart, keeping the heart outside of the thorax without closing off the blood circulation. A thread soaked with diluted disinfectant solution is placed as a loop around the apex of the heart and tightened so that the apical third of both ventricles is tied off. The degree of tightening of the loop is essential. Complete interruption of blood supply to the apical third resulting in necrosis has to be avoided as well as the loop's slipping off. Technical skill is necessary to place the loop around the beating heart into the correct position. After removal of the clamp, the heart is placed back, the incision between the fourth and fifth costal rib closed, and the musculus pectoralis placed over the wound. Intrathoracal air forming a pneumothorax is removed by pressure on both sides of the thorax. After application of an antibiotic emulsion, the skin wound is closed. The surgical procedure has to be finished within a short period of time.

The animals develop symptoms of severe congestive heart failure with a death rate of 80 % within 14 days. Lung weight and relative heart weight are significantly increased. Exudate in the thorax cavity and ascites amount between 3.5 and 7.5 ml with extreme values of 17.5 ml. Lung edema and liver congestion are found histologically. Peripheral edema and preterminal dyspnea and tachypnea are observed. When treated with various doses (0.1–100 μg/kg) of cardiac glycosides s.c. or i.m. over a period of 14 days, the symptoms of cardiac insufficiency, e.g., volumes of transudate as well as death rate, are dose-dependent diminished.

Evaluation

From survival rate, ED_{50} values of cardiac glycosides can be calculated which are in the same dosage range as therapeutic doses in man.

Critical Assessment of the Method

The experimental model in guinea pigs reflects very closely the symptoms of cardiac insufficiency in man, e.g., lung congestion, hydrothorax, liver congestion, ascites, peripheral edema, and cardiac hypertrophy. The therapeutic potency of cardiac glycosides can be evaluated with this method. Additional factors being known to enhance the symptoms of congestive heart failure in man, like salt load and diphtheria toxin, further increase mortality and hydropic symptoms. The method can be used for special purposes; however, it needs considerable training and technical skill.

Modifications of the Method

Siri et al. (1989, 1991) produced left ventricular hypertrophy in the guinea pig by gradually increasing ventricular afterload. A mildly constricting band was placed around the ascending aorta of very young guinea pigs (225–275 g). With growth to 500–1,000 g, left ventricular systolic pressure increased and ventricular hypertrophy developed. Only some of the animals developed dyspnea and severe ventricular dysfunction.

Kiss et al. (1995) studied the effects on Ca^{2+} transport and mechanics in compensated pressure-overload hypertrophy and congestive heart failure in guinea pigs. The descending aorta was banded for 4 and 8 weeks in adult guinea pigs.

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Tweedle et al. (1995) assessed subrenal banding of the abdominal aorta as a method of inducing cardiac hypertrophy in the guinea pig.

Pfeffer et al. (1987) induced myocardial infarction in **rats** by ligation of the left coronary artery and found hemodynamic benefits and prolonged survival with long-term captopril therapy.

Acute ischemic left ventricular failure can be induced in anesthetized **dogs** by repeated injections of plastic microspheres into the left coronary artery (see chapter "► Coronary Drugs", section "Acute Ischemia by Injection of Microspheres in Dogs").

Huang et al. (1997) created congestive heart failure in **sheep** by selective sequential intracoronary injection of 90 μm microspheres under 1.5 % isoflurane injection.

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Cardiomyopathic Syrian Hamster

Purpose and Rationale

Cardiomyopathy in Syrian hamsters has been described by Bajusz et al. (1966), Bajusz and Lossnitzer (1968), Bajusz (1969), Bajusz et al. (1969a, b), Homburger and Bajusz (1970), and Gertz (1972). The disease originates from an autosomal, recessively transmissible disorder, which leads to degenerative lesions in all striated muscles and in particular in the myocardium. Histopathological changes consist of myocytolytic necrosis followed by fibrosis and calcification. The evolution of the cardiomyopathic disease can be characterized by five distinct phases: a prenecrotic stage, in which no pathology is evident, a time of active myocytolysis and cellular necrosis, a phase of fibrosis and calcium deposition, an

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overlapping period of reactive hypertrophy of the remaining viable myocytes, and a final stage of depressed myocardial performance and failure.

Procedure

The model of cardiomyopathy in Syrian hamsters has been used by several authors. One has to note that several strains of cardiomyopathic hamsters have been used: strain Bio 53:58 by Capasso et al. (1989, 1990) and by Chemla et al. (1992, 1993), strain BIO 14.6 by Tapp et al. (1989) and by Sen et al. (1990), strain CHF 146CM by van Meel et al. (1989) and by Haleen et al. (1991), strain BIO82.62 by ver Donck et al. (1991), strain J-2-N by Kato et al. (1992), and strain CHF 147 by Desjardins et al. (1989) and Hanton et al. (1993).

Various experimental protocols have been described. Most authors use survival rate and heart weight as end point (e.g., van Meel et al. 1989; ver Donck et al. 1991; Hanton et al. 1993). Generally, the experiments are started with animals at an age of 120–200 days.

Capasso et al. (1989, 1990) studied the mechanical and electrical properties of cardiomyopathic hearts of Syrian hamsters using isolated left ventricular posterior papillary muscles.

Tapp et al. (1989) tested stress-induced mortality in cardiomyopathic hamsters by five consecutive daily 2-h periods of supine immobilizations at 4 °C.

Sen et al. (1990) tested the inotropic and calcium kinetic effects of calcium channel agonists and antagonists in primary cultures of isolated cardiac myocytes.

Haleen et al. (1991) tested the effects of an angiotensin-converting-enzyme inhibitor not only on survival but also on left ventricular failure in the isolated Langendorff heart by measurement of left ventricular end-diastolic pressure, dP/dt_{max}, and mean coronary flow.

Dixon et al. (1997) tested the effect of an AT_1 receptor antagonist on cardiac collagen remodeling in the cardiomyopathic Syrian hamster.

In addition to the effects on left ventricular papillary muscles strips, Chemla et al. (1992) tested the effects on diaphragm contractility in the cardiomyopathic Syrian hamster.

Whitmer et al. (1988) and Kuo et al. (1992) tested sarcolemmal and sarcoplasmatic reticulum calcium transport in the cardiomyopathic Syrian hamster.

Nigro et al. (1997) identified the Syrian hamster cardiomyopathy gene.

Tanguay et al. (1997) tested the coronary and cardiac sensitivity to a vasoselective benzothiazepine-like calcium antagonist in isolated, perfused failing hearts of Syrian hamsters.

Bilate et al. (2003) recommended the Syrian hamster as a model for the dilated cardiomyopathy of Chagas disease. Female hamsters were infected via the intraperitoneal route with *Trypanosoma cruzi* Y strain blood trypomastigotes. Survival was monitored, echocardiography was performed after 4 and 12 months, and histopathological examinations were carried out at the end of the study period.

Critical Assessment of the Method

Positive effects of various drugs have been found in the cardiomyopathic hamster, such as cardiac glycosides, inotropic compounds, beta-blockers, calcium antagonists, and ACE inhibitors. The specificity of the effects has to be challenged.

Modifications of the Method

The **tight skin (TSK) mouse** is a genetic model of pulmonary emphysema connected with right ventricular hypertrophy (Martorana et al. 1990; Gardi et al. 1994).

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Cardiac Failure in Rabbits

Purpose and Rationale

Rabbit models of heart failure were reviewed by Muders and Elsner (2000).

Rapid pacing was used by Masaki et al. (1994), Porsa et al. (1994), Eble et al. (1998), Li et al. (2003), and Rose et al. (2005); coronary artery ligation by Pennock et al. (1997), Currie and Smith (1999), Romanic et al. (2001), and Miller et al. (2004); combined pressure and volume overload by Ezzaher et al. (1991), Mohammadi et al. (1997), Dekker et al. (1998), and Baartscheer et al. (2003a, b); aortic insufficiency and aortic constriction by Bouanani et al. (1991) and Pogwizd et al. (1999); regurgitation after damage of the mitral valve by Gunawardena et al. (1999); and regurgitation after aortic valve destruction by Magid et al. (1988, 1994), Yoshikawa et al. (1993), King et al. (1997), Liu et al. (1998), and Luchner et al. (2001) used a rabbit model of progressive left ventricular dysfunction to investigate differential expression of cardiac atrial natriuretic peptide and brain natriuretic peptide. Ventricular pacing-induced heart failure could be induced with a transvenously implanted pacemaker system.

Procedure

Male rabbits (chinchilla bastard) underwent implantation of a programmable cardiac pacemaker (Medtronic Minix 8340, Minneapolis, Mn., USA). Under anesthesia (ketamine 60 mg/kg xylazine 5 mg/kg i.m.), the right internal jugular vein was dissected and cannulated with a single-lumen central venous catheter (Braun, Germany). The catheter was then advanced into the right ventricle under pressure guidance. A transvenous screw-in pacemaker lead (Medtronic) was advanced through the catheter into the ventricular apex and implanted endocardially. The pacemaker was implanted subcutaneously into the right abdominal wall, and the pacemaker lead was connected subcutaneously with the pacemaker. Rapid ventricular pacing-induced heart failure could be induced with a transvenously implanted pacemaker system. All rabbits were allowed to recover for at least 10 days after surgery before the pacemaker was started for the induction of heart failure. Proper pacemaker function was checked intraoperatively, at the time of programming, and subsequently all 10 days.

Rabbits (CHF group) underwent pacing with a stepwise increase of stimulation frequencies over 30 days. During the first 10 days, animals were paced at 330 beats/min (bpm). This protocol results in ELVD, as defined by significant LV systolic dysfunction with cardiac enlargement and decreased perfusion pressure, but no clinical signs of heart failure. The pacing rate was then increased to 360 bpm for 10 days and 380 bpm for another 10 days, and ELVD evolved to CHF with further cardiac enlargement and further decreased perfusion pressure together with clinical signs of fluid retention (ascites). At baseline (control), after being paced at 330 bpm for 10 days (ELVD) and at the end of the protocol (CHF), conscious arterial pressure was measured invasively via the medial ear artery and a 2-D-guided M-mode echocardiogram was obtained. At the end of the pacing protocol, rabbits were killed by i.v. euthanasia and tissue was rapidly harvested. Hearts were trimmed on ice, snap frozen in liquid nitrogen, and stored at −80 °C until further processing.

Echocardiography

A long- and short-axis echocardiogram (HP Sonos 5500, 12 MHz probe) was performed under light sedation (5 mg midazolam i.m.) in a supine position from the left parasternal window. LV end-diastolic (LVEDd) and end-systolic (LVESd) dimensions and diastolic and systolic thickness of the left ventricular anterior wall (AEDth and AESth) and posterior wall (PEDth and PESth) as well as left atrial diameter (LAd) were determined from three repeated 2-D-guided M-mode tracings using the ASE convention. From those measurements, fractional shortening (FS) was calculated as

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$$\mathrm{FS} = \frac{(\mathrm{LVEDd} - \mathrm{LVESd})}{\mathrm{LVEDd}}.$$

Analytical Methods

For analysis of cardiac natriuretic peptide expression, mRNA was extracted from all atrial and left ventricular samples utilizing a commercial kit (Fasttrack, Invitrogen).

As a probe for brain natriuretic peptide (BNP), a 750-bp *Eco*R1/*Hind*III DNA restriction fragment containing the gene for rabbit BNP was used.

Evaluation

Results of the quantitative studies were expressed as mean ± SEM. Comparisons between the control, ELVD, and CHF groups were performed by analysis of variance (ANOVA) followed by Fisher's least significant difference test. Comparison between the atrial and LV tissues as well as between atrial natriuretic peptide (ANP) and BNP was performed by paired Student's *t*-test. Statistical significance was defined as $P < 0.05$.

Modifications of the Method

Arnolda et al. (1985) studied adriamycin cardiomyopathy in the rabbit.

Klimtova et al. (2002) performed a comparative study of chronic toxic effects of daunorubicin and doxorubicin in rabbits.

Alexander et al. (1993) studied electrographic changes following coronavirus-induced myocarditis and dilated cardiomyopathy in rabbits.

Sanbe et al. (2005) described a transgenic model for human troponin I-based hypertrophic cardiomyopathy in the rabbit.

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Cardiac Failure in Dogs

Purpose and Rationale

Several methods are described, to induce congestive heart failure in dogs, such as rapid ventricular pacing (Armstrong et al. 1986; Freeman et al. 1987; Wilson et al. 1987; Komamura et al. 1992, 1993; Perreault et al. 1992; Travill et al. 1992; Cheng et al. 1993; Redfield et al. 1993; Cory et al. 1994; Kiuchi et al. 1994; Ohno et al. 1994; Vatner et al. 1994; Wang et al. 1994; Williams et al. 1994; Eaton et al. 1995; Spinale et al. 1995; Wolff et al. 1995; Zile et al. 1995; Ravens et al. 1996; Shinbane et al. 1997; O'Rourke et al. 1999; Winslow et al. 1999).

Luchner et al. (1996) assessed circulating, renal, cardiac, and vascular angiotensin II in a canine model of rapid ventricular pacing-induced heart failure that evolves from early left ventricular dysfunction to overt congestive heart failure.

Procedure

Male mongrel dogs underwent implantation of a programmable cardiac pacemaker (Medtronic). Under pentobarbital sodium anesthesia and artificial respiration, the heart was exposed via a small left lateral thoracotomy and pericardiotomy, and a screw-in epicardial pacemaker lead was implanted into the right ventricle. The pacemaker was implanted subcutaneously into the left chest wall and connected to the pacemaker lead. The dogs were allowed to recover for at least 10 days after surgery before the pacemaker was started. During the first 10 days, dogs were paced at 180 beats/min (bpm), resulting in early left ventricular dysfunction as defined by significant systolic dysfunction with decreased cardiac output, cardiac enlargement, and increased filling pressures but maintained systemic perfusion pressure and renal sodium excretion and no clinical signs of heart failure. The pacing rate was then increased weekly to 200, 210, 220, and 240 bpm, and early left ventricular dysfunction evolved to overt congestive heart failure with avid sodium retention and clinical signs of congestion. At baseline (control), after dogs had been paced at 180 bpm for 10 days and at the end of the protocol (overt CHF), urine was collected for measurement of sodium excretion; conscious mean arterial pressure was measured via a port catheter; a 2-D-guided M-mode echogram was obtained; and arterial blood was drawn. Cardiac filling pressures and cardiac output were measured by the thermodilution method at baseline and at the end of the protocol. Arterial blood was collected in EDTA tubes for measurement of ANP, BNP, cGMP, PRA, aldosterone, and Ang II. After euthanasia, hearts were rapidly trimmed and left ventricles weighted for calculation of the index LV weight to body weight.

Evaluation

Results were expressed as mean $\pm$ SE. Comparison between the control, early LV dysfunction, and overt CHF were performed by ANOVA followed by Fisher's least significant difference test.

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Modifications of the Method

Kleaveland et al. (1988) and Nagatsu et al. (1994) used the technique of experimental **mitral regurgitation** in dogs to induce left ventricular dysfunction. A 30-cm, 7-F sheath was introduced across the aortic valve through the carotid artery. A urologic calculus retrieval forceps was advanced through the sheath to the mitral valve apparatus and was used to sever chordae tendineae. When pulmonary capillary wedge pressure rose to 20 mmHg and forward stroke volume was reduced to 50 % of its baseline, a ventriculogram was performed to confirm angiographically that severe mitral regurgitation had been created.

Dell'Italia et al. (1995) and Su et al. (1999) induced mitral regurgitation by percutaneous chordal rupture in dogs.

Kinney et al. (1991) published a method to induce acute, reversible tricuspid insufficiency in anesthetized dogs. A wire spiral is advanced through the atrioventricular canal from the right atrium. The spiral causes regurgitation by preventing complete apposition of the valve leaflets while permitting retrograde flow to occur through the spiral lumen. The degree of regurgitation can be controlled by the use of spirals of different size. Creation of tricuspid insufficiency was demonstrated by onset of right atrial pressure V waves, a ballooning of the right atrium during ventricular systole, palpation of an atrial thrill, or color Doppler echocardiography. The model is reversible and allows repeated trials of various grades of regurgitation.

Carlyle and Cohn (1983) described a non-chirurgical model of chronic left ventricular dysfunction. The method is accomplished by repetitive DC shock with a guidewire introduced percutaneously and positioned in the left ventricle along the intraventricular septum and an external paddle at the left ventricular apex.

McDonald et al. (1992) produced localized left ventricular necrosis without obstruction of the coronary blood flow in dogs by transmyocardial direct-current shock.

Sabbah et al. (1991, 1993, 1994) and Gengo et al. (1992) produced chronic heart failure in dogs by multiple sequential intracoronary **embolizations with microspheres**. The dogs underwent three to nine intracoronary embolizations with polystyrene latex microspheres (70–102 μm in diameter) performed 1–3 weeks apart. Embolizations were discontinued when left ventricular ejection fraction was less than 35 %. Vanoli et al. (2004) used multiple coronary microembolizations in dogs, whereby three to nine embolizations were performed 1 week apart. The first three embolizations consisted of 2 ml of microsphere suspension injected subselectively into either the left anterior descending or left circumflex coronary artery in an alternating fashion. Subsequent embolizations consisted of 3–6 ml of microspheres divided equally between the left anterior descending or left circumflex coronary artery until LV ejection fraction was <35 %.

Magovern et al. (1992) described a canine model of left ventricular dysfunction caused by five weekly intracoronary infusions of **adriamycin**.

Koide et al. (1997) described premorbid determinants of left ventricular dysfunction in a model of gradually induced pressure overload in dogs. Mongrel dogs were studied through 8 weeks of gradually imposed ascending aortic constriction with the use of a **novel banding technique**. During banding, an initial gradient of 30 mmHg was created. Before banding, at 2, 4, and 6 weeks after banding, hemodynamics and left ventricular mechanics were examined at cardiac catheterization; then the pressure overload was increased by tightening the band.

Valentine et al. (1988) and Devaux et al. (1993) described **X-linked muscular dystrophy in dogs** with cardiac insufficiency similar to Duchenne muscular dystrophy in men and recommended this as an animal model for cardiac insufficiency.

Bilateral renal wrapping model in adult male dogs (20–26 kg) has been described previously (Page 1939; Hart et al. 2001; Maniu et al. 2002); in this model, the kidneys were wrapped with silk without

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constriction of renal vessels. Increased in systolic blood pressure and LV mass index was observed at 5 weeks post renal wrapping. At 12 weeks post renal wrap, an increase in LVEDP was observed. LV end-diastolic volume, ejection fraction, stroke volume, and cardiac output were not changed in this model. No changes in circulating angiotensin II, endothelin, catecholamines, and plasma renin activity were also noted. A modification of this method has been published by Hayashida et al. (1997, 1998); in these studies only the left kidney was wrapped. The dogs developed hypertension and diastolic dysfunction with increased LV weight/body weight ratio and LVEDP and without significant changes in fractional shortening or LV diameters an increased Ang II levels.

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Cardiac Failure in Pigs

Purpose and Rationale

Cardiac failure was studied in pigs using several experimental procedures.

Chow et al. (1990) recommended rapid ventricular pacing in pigs as an experimental model of congestive heart failure.

Farrar et al. (1993) studied pacing-induced dilated cardiomyopathy in pigs. Congestive heart failure was produced by rapid ventricular pacing at 230 bpm for 1 week.

Spinale et al. (1990a, b, 1991, 1992) examined the consequences of chronic supraventricular tachycardia on various parameters of ventricular dysfunction and subendocardial changes in pigs.

Carroll et al. (1995) investigated gene expression in a swine model of ventricular hypertrophy during pressure overload.

Multani et al. (2001) studied long-term angiotensin-converting enzyme and angiotensin I receptor inhibition in pacing-induced heart failure in pigs. Heart failure was induced by rapid atrial pacing (240 bpm for 3 weeks).

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Kassab et al. (1993, 2000) investigated remodeling of right ventricular branches after hypertrophy in pigs.

Krombach et al. (1999) studied the effects of amlodipine in congestive heart failure in pigs at rest and after treadmill exercise.

Procedure

Left thoracotomy was performed in Yorkshire pigs under anesthesia. Catheters connected to a vascular access port were placed in the thoracic aorta, the pulmonary artery, and the left atrium. The access ports were then placed in a subcutaneous pocket. A 20-mm flow probe was placed around the pulmonary artery immediately distal to the pulmonary catheter and the electrical connection exteriorized through the thoracolumbar fascia. A shielded stimulating electrode was sutured onto the left atrium, connected to a programmable pacemaker, and buried in a subcutaneous pocket. The thoracotomy was closed in layers and the pleural space evacuated of air. After a 14–21-day recovery, measurements were performed under normal resting conditions and after exercise. The pacemakers were activated to 240 bpm for a period of 21 days. During the last 3 days, one group was treated with drug, the other served as control. At the day of the study, electrocardiograms were performed, and the pacemakers deactivated. After a 30-min stabilization period, 2-D and M-mode echocardiographic studies were used to image the left ventricle from the parasternal approach. Left ventricular fractional shortening was calculated as (end-diastolic dimension – end-systolic dimension)/diastolic dimension and was expressed as a percentage. The access ports were entered and pressures obtained using externally calibrated transducers. The flow probe was connected to a digital flowmeter. From the digitized flow signal, stroke volume was computed on a beat-to-beat basis and averaged for a minimum of 25 ejections. Pulmonary and systemic vascular resistances were computed as the mean pressure divided by cardiac output multiplied by the constant 80 to convert to resistance units of dyne $\cdot$ s $\cdot$ cm^{-5}. Samples were drawn from the pulmonary artery and atrial catheters for measurement of oxygen saturation and hemoglobin content. The plasma samples were assayed for renin activity, endothelin concentration, and catecholamine levels.

Evaluation

Results were presented as mean $\pm$ SEM. Pairwise tests of individual group means were compared using Bonferroni probabilities.

Modifications of the Method

Zhang et al. (1996) studied functional and bioenergetic consequences of postinfarction left remodeling in a porcine model. Proximal left coronary artery occlusion was used to generate a myocardial infarction in young pigs. The animals were then followed over several months while remodeling of the left ventricle developed. Left ventricular wall thickness, ejection fraction, and wall stress were measured by MR-I. Myocardial ATP, creatine phosphate, and inorganic phosphate levels were measured by spatially localized ^{31}P-NMR spectroscopy, and regional myocardial blood flow was measured with radioactive microspheres.

Procedure

MRI Protocols

All MRI studies were performed on the standard Siemens Medical System VISION operating at 1.5 T. The animals were anesthetized with sodium pentobarbital. A catheter was placed into the femoral artery and advanced into the LV chamber for LV pressure recording. Animals then were placed on their left side in a Helmholtz coil with a diameter of 18 cm, which was used to improve signal to noise. To compute LV wall stress, the image acquisition was triggered by the LV pressure through the fluid-filled LV

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catheter. All of the imaging sequences were synchronized to the LV pressure trace. The electronic LV pressure signal was recorded and fed to a comparator set to a threshold level of 10 % of the upslope of the LV pressure curve at the beginning of systole. The signal from the comparator was sent to a pulse former and then fed to the ECG port of the magnetic resonance system, where it was treated like the standard electrographic input to run the pulse sequences. Scout images were taken in the axial plane with a single-shot, ultrafast gradient echo sequence (McDonald et al. 1992; Wilke et al. 1993; Geiger et al. 1995). From the axial image, both horizontal and vertical long-axis images were obtained. By alternating back and forth several times, a true vertical long axis of the left ventricle was obtained. From the long-axis scout image, short-axis segmented cine turboflash slices were prescribed to cover the myocardium from apex to base. The double oblique, short-axis turboflash images cover the heart from apex to base with a slice thickness of 10 mm, with no interslice gap.

MRI Cine Technique

The parameters of the segmented cine sequence were TR/TE/flip angle = 33 ms/6.1 ms/25° with an FOV = 17.5 cm and a matrix of 87 × 128 (pixel size, 2 × 1.4 mm) and slice thickness of 7–10 mm (Atkinson and Edelman 1991). The sequence used segmented k-space acquisition such that three phase-encoded lines were gathered per cardiac phase per heartbeat. Total image acquisition required approximately 52 heartbeats for each slice location. The temporal image resolution (data acquisition window) of this sequence was 33 ms per cardiac image. Each myocardial level took <1.5 min to acquire, since two acquisitions were used and the average heart rate of the animals was 120 bpm. The average number of short-axis slices needed to image the entire myocardium from apex to base was 6–8. This 10-min protocol provided high signal-to-noise cine sequences covering the entire heart.

Spin-Echo Images

To obtain high-resolution anatomic heart images, multislice, single-phase spin-echo images trigged in the systolic phase were acquired to cover the entire heart. These images permitted the precise delineation of the extent of the scar region of the heart. Images were taken with a slice thickness of 5 mm and a FOV of 17.5 cm, resulting in a true spatial resolution of 2 × 1.4 mm pixel size. The TR for this sequence equals the RR interval (500 ms) and the echo time TE was set to 30 ms. Total measurement time for an average of 10–14 slices was 5 min.

Image Analysis of the MRI Cine Studies

The imaging data were archived to optical disk and copied to a SUN SPARC 10 workstation for evaluation with the use of an automatic segmentation program (ImageView, Siemens Cooperate Research). The program is based on robust deformable models of endocardial and epicardial border segmentation of ventricular boundaries in cardiac magnetic resonance images. This segmentation technique has been combined with a user interface that allows one to load, sort, visualize, and analyze a cardiac study in <20 min. The segmentation algorithm is based on the steepest descent as well as dynamic programming strategies integrated via multiscale analysis for minimizing the energy function of the resulting contour. The ventricular boundaries are used to construct a three-dimensional model for visualization and to compute hemodynamic parameters. Automatic segmentation of endocardial and epicardial boundaries was performed for calculation of ventricular volumes, EF, LV diastolic and systolic volumes, and absolute myocardial mass from multislice, multiphase magnetic resonance cine images. Starting with a user-specified approximate boundary or an interior point of the ventricle for one starting image in one slice, the algorithm generated automatic contours corresponding to the epicardium and the endocardium and automatically propagated them to other slices in the cardiac phase (spatial propagation) and to other phases for a given slice location (temporal propagation) of the cardiac study. The observer

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then could make some manual corrections to the six or seven pairs of contours in the first column of the temporal-spatial matrix. Manual modifications generally were made on the apex and base levels.

Evaluation

Mean LV wall thickness for each short-axis ring was averaged from three measurements of the remote zone (anterior wall and septum wall). The thickness of the scar was averaged from three measurements of the scar area. LVSA measurement in each slice was computed by subtracting the total area enclosed by the endocardium from that enclosed by the subepicardium; the resultant area was multiplied by the slice thickness to obtain the volume of each slice; the total LV mass volume was calculated by adding up the volumes of all the short-axis slices. The total LVSA was obtained by dividing the total LV wall mass volume by the mean of LV wall thickness of each slice. Similarly, the LVSSA was obtained by dividing the total scar volume, which was the sum of the scar volume of each short axis, by the mean of the scar thickness of each short axis. LV mass was computed by the total LV wall mass volume multiplied by 1.05 (specific gravity of myocardium) to calculate the LV mass. The LV end-diastolic volume (V_d) and end-systolic volume (V_s) of each slice were represented by the area enclosed by the endocardium. The total LV volume was computed by adding the volumes of all slices. LVEF was calculated by $100 \times (V–V_s)/V_d\%$. Interobserver and intraobserver errors for the calculations of LV mass and LV volumes have been shown to be <3 mg and 3 ml, respectively (McDonald et al. 1994). Meridional wall stress was computed from the LV pressure and simultaneously obtained short-axis view of LV MRI (LV cavity diameter and average thickness the remote LV wall) as described by Grossman et al. (1975).

Spatially Localized ^{31}P-NMR Spectroscopic Technique

Measurements were performed in a 40-cm-bore, 4.7-T magnet interfaced with a SISCO (Spectroscopy Imaging Systems Corporation) console. The LV pressure signal was used to gate NMR data acquisition to the cardiac cycle, while respiratory gating was achieved by triggering the ventilator to the cardiac cycle between data acquisitions (Robitaille et al. 1990). ^{31}P and ^{1}H-NMR frequencies were 81 and 200.1 MHz, respectively. Spectra were recorded in late diastole with a pulse repetition time of 6–7 s. This repetition time allowed full relaxation for ATP and P_i resonances and ≈90 % relaxation for the CP resonance (Zhang and McDonald 1995). CP resonance intensities were corrected for this minor saturation; the correction factor was determined for each heart from two spectra recorded consecutively without transmural differentiation, one with 15-s repetition time to allow full relaxation and the other with the 6–7-s repetition time used in all the other measurements.

Radiofrequency transmission and signal detection were performed with a 25-mm-diameter surface coil. The coil was cemented to a sheet of silicone rubber 0.7 mm in thickness and ≈50 % larger in diameter than the coil itself. A capillary containing 15 μl of 3 M phosphonoacetic acid was placed at the coil center to serve as a reference. The proton signal from water detected with the surface coil was used to homogenize the magnetic field and to adjust the position of the animal in the magnet so that the coil was at or near the magnet and gradient isocenters. This was accomplished with a spin-echo experiment and a readout gradient. The information gathered in this step also was used to determine the spatial coordinates for spectroscopic localization. Chemical shifts were measured relative to CP, which was assigned a chemical shift of −2.55 ppm relative to 85 % phosphoric acid at 0 ppm.

Spatial localization across the LV wall was performed with the RAPP-ISIS/FSW method (Hendrich et al. 1991). Signal origin was restricted with the use of B_0 gradients and adiabatic inversion pulses to a column coaxial with the surface coil perpendicular to the LV wall. The column dimensions were 17 × 17 mm. Within this column, the signal was further localized using the B_1 gradient to five voxels centered about 45°, 60°, 90°, 120°, and 135° spin rotation increments. FSW localization used a nine-term Fourier series expansion. The Fourier coefficients, the number of free induction decays acquired for each

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term in the Fourier expansion, and the multiplication factors used to construct the voxels have been reported previously. The position of the voxels relative to the coil was set using the B_1 magnitude at the coil center, which was experimentally determined in each case by measurement of the 90° pulse length for the phosphonoacetic acid reference located in the coil center. Each set of spatially localized transmural spectra was acquired in 10 min. A total of 96 scans was accumulated within each 10-min block.

Evaluation

Resonance intensities were quantified with the use of integration routines provided by the SISCO software. ATPγ resonance was used for ATP determination. Since data were acquired with the transmitter frequency being positioned between the ATPγ and CP resonance, the off-resonance effects on these peaks were negligible. The numeric values for CP and ATP in each voxel were expressed as ratios of CP/ATP. P_i levels were measured as changes from baseline values (ΔP_i) with the use of integrals obtained in the region covering the P_i resonance.

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Cardiac Failure in Sheep

Purpose and Rationale

Various methods have been used to induce cardiac failure in sheep: pressure overload after aortic banding (Aoyagi et al. 1993; Charles et al. 1996), volume loading after myocardial infarction (Charles et al. 2003), rapid ventricular pacing (Rademaker et al. 1997, 2002, 2005; Byrne et al. 2002; Moreno et al. 2005), coronary microembolization (Huang et al. 2004; Monreal et al. 2004), and thrombus-induced heart failure (Chandrakala et al. 2013).

Rademaker et al. (2002) studied combined angiotensin-converting enzyme inhibition and adrenomedullin in an ovine model of heart failure induced by rapid ventricular pacing.

Procedure

Surgical Preparation

Coopworth ewes (38 ± 47 kg) were instrumented via a left lateral thoracotomy. Under general anesthesia (induced by 17 mg/kg thiopentone; maintained with halothane/nitrous oxide), two polyvinyl chloride catheters were inserted in the left atrium for blood sampling and left atrial pressure (LAP) determination; a Konigsberg pressure-tip transducer was inserted in the aorta to record mean arterial pressure (MAP); an electromagnetic flow probe was placed around the ascending aorta to measure cardiac output (CO); a

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7-French Swan-Ganz catheter was inserted in the pulmonary artery for infusions; and a 7-French His bundle electrode was stitched subepicardially to the wall of the left ventricle for left ventricular pacing. All leads were externalized through incisions in the back. A bladder catheter was inserted per urethra for urine collections.

The animals were allowed to recover for 14 days before commencing the study protocol. During the experiments, the animals were held in metabolic cages, had free access to water, and ate a diet of chaff and sheep pellets (containing 40 mmol/day sodium and 200 mmol/day potassium). A further 40 mmol of sodium was administered orally daily as NaCl tablets using an applicator.

Study Protocol

Heart failure was induced by 7 days of rapid left ventricular pacing (225 bpm) (Rademaker et al. 1997) and maintained by continuous pacing for the duration of the study. On four separate days with a rest day between each, the sheep received, in random order, a vehicle control (Haemaccel), human adrenomedullin alone (50 ng/min per kg infusion for 3 h), an ACE inhibitor alone (captopril: 25 mg bolus + 2 mg/h infusion for 3 h), and both agents combined. Infusions were administered in a total volume of 60 ml via the pulmonary artery catheter, commencing at 10:00 h.

Mean arterial pressure, left atrial pressure, cardiac output, and calculated total peripheral resistance (CTPR = mean arterial pressure/cardiac output) were recorded at 15-min intervals in the 1 h prior to infusion (baseline) and at 15, 30, 45, 60, 90, 120, and 180 min during both the 3-h infusion and post-infusion periods. Hemodynamic measurements were determined by online computer-assisted analysis.

Blood samples were drawn from the left atrium at 30 min and immediately pre-infusion (baseline) and at 30, 60, 120, and 180 min during the 3-h infusion and post-infusion periods. Samples were taken into tubes on ice, centrifuged at 3,939 g for 10 min at 4 °C, and stored at either −20 or −80 °C before assay for immunoreactive (ir-) adrenomedullin, cAMP, plasma renin activity, angiotensin II, aldosterone, atrial natriuretic peptide, brain natriuretic peptide, endothelin-1, catecholamines, and cortisol.

All samples from individual animals were measured in the same assay to avoid inter-assay variability. Plasma electrolytes and hematocrit were measured in every sample taken. Urine volume and samples for the measurement of urine cAMP, sodium, potassium, and creatinine excretion were collected every 1 h. Creatinine clearance was calculated as urine creatinine/plasma creatinine.

Evaluation

Results are expressed as mean ± SEM. Baseline hemodynamic and hormone values represent the means of the four and two measurements, respectively, made in the 1 h immediately pre-infusion. Statistical analysis was performed by repeated-measures ANOVA. Baseline data from all treatments were compared. Treatment- and time-related differences between all four study limbs were determined using a two-way ANOVA (treatment–time interactions are quoted in the text). Statistical significance was assumed when $P < 0.05$.

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Cardiac Failure in Monkeys

Purpose and Rationale

Several authors used monkeys for studies of cardiac failure. Hollander et al. (1977) investigated the role of hypertension in ischemic heart disease in the **cynomolgus monkey** with coarctation of the aorta. Sieber et al. (1980) studied cardiotoxic effects of adriamycin in **macaques**.

Various studies were performed by the group of Hoit and Walsh in **baboons** (Hoit et al. 1995a, b, 1997a, b; Khoury et al. 1996). Hoit et al. (1997a) studied the effects of thyroid hormone on cardiac β-adrenergic responsiveness in conscious baboons.

Procedure

Animal Instrumentation

Adult male baboons (*Papio anubis*) weighing 21–30 kg were pre-instrumented for physiological monitoring in a lightly anesthetized, sedated state. Animals were pre-instrumented with a Konigsburg micromanometer and a polyvinyl catheter in the LV apex, miniaturized sonomicrometer pairs (3 MHz,

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6 mm) across the LV anteroposterior minor axis, a polyvinyl catheter in the right atrium for central venous access, and pacing wires on the right atrial appendage. Wires and tubes were tunneled subcutaneously into the interscapular area for later use. Postoperative pain was reduced by the use of Buprenex (0.01 mg/kg i.m., q 6 h), and postoperative antibiotic (Monocid 25 mg/kg) was administered for 5 days to reduce the risk of infection. Baseline hemodynamic studies were performed after a minimum of 1 week for postoperative recovery.

Hemodynamic Data Acquisition and Analysis The micromanometers and fluid-filled catheters were calibrated with a mercury manometer. Zero drift of the micromanometer was corrected by matching the LV end-diastolic pressure measured simultaneously through the LV catheter. The fluid-filled LV catheter was connected to a pre-calibrated Statham 23-dB transducer with zero pressure at the level of the mid-right atrium. The transit time of ultrasound between the ultrasonic dimension crystals was measured with a multichannel sonomicrometer (Triton Technology) and converted to distance assuming a constant velocity of sound in blood of 1.55 mm/ms.

The analog LV dP/dI signal was obtained online by electronic differentiation of the high-fidelity LV pressure signal. τ was derived from the high-fidelity LV pressure tracing by the method of Weiss et al. (1976), which assumes a monoexponential decay of LV pressure to a zero asymptote and has been shown to be directionally equivalent to other mathematical approaches for quantification of isovolumic pressure decay. τ is equal to the time in milliseconds for LV pressure to decay to $1/e$; thus, decreases in τ reflect improved isovolumic ventricular relaxation.

Fractional shortening of the LV minor axis was calculated as (EDD–ESD)/EDD, where EDD is the LV end-diastolic dimension and ESD is the LV end-systolic dimension. LV end-diastole was defined as the time in which LV dP/d$t$max increased by $\geq$150 mmHg/s for 50 ms, and LV end-systole was defined as the time of the maximum ratio of LV pressure to LV minor-axis dimension. LV volumes were derived from minor-axis diameter (D) measurements:

$$\text{LV volume} = \frac{\pi}{6(D)^3}.$$

V_{cf} was calculated as LV fractional shortening divided by LV ejection time; LV ejection time was defined as the time from peak-positive to peak-negative dP/dt.

Analog signals for high-fidelity and fluid-filled LV pressures, LV short-axis dimension, LV dP/dt, and the ECG were recorded online on a Gould multichannel recorder at 25 and 100 mm/s paper speed and digitized through an analog-to-digital board (dual control systems) interfaced to an IBM AT computer at 500 Hz and stored on a floppy disk. Data were analyzed using an algorithm and software developed in our laboratory. Steady-state data were acquired over 5–10 s during spontaneous respiration and averaged.

Experimental Protocols

Hemodynamic studies were performed a minimum of 1 week after instrumentation and were repeated after 22–30 (26.8 $\pm$ 2.7) days of thyroid T_4 administration. Animals were tranquilized with Valium (1–5 mg) and ketamine (100 mg), and cholinergic blockade was achieved with atropine (0.4–0.8 mg i.v.); additional ketamine was administered as necessary, to a maximum cumulative dose of 40 mg/kg. Animals were atrially paced at a rate 40–50 % greater than the control heart rate in order to obtain data at matched heart rates after thyrotoxicosis was produced.

Dobutamine Group

After hemodynamic stability was ensured and baseline data were recorded, intravenous dobutamine was infused at 5-min intervals at upwardly titrated rates of 2.5, 5.0, 7.5, and 10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to

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examine the effects of β_1-adrenergic stimulation. The dose range of catecholamine for these studies was chosen to alter inotropic and lusitropic states without causing an untoward increase in heart rate. Steady-state hemodynamic measurements were made during minutes 4 and 5 of each infusion period. At each level, the pacemaker was briefly turned off to determine the effect of dobutamine on the heart rate.

Four of the animals in this group were studied with incremental pacing both before and after β-adrenergic blockade with esmolol (0.3 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} i.v.). The pacing protocol and the results from a larger group of animals studied before β-adrenergic blockade were detailed in a previous report. Briefly, atrial pacing was instituted at a rate above the intrinsic heart rate to avoid competing rhythms and was increased at 0.2-Hz increments until the critical heart rate was achieved. The critical heart rate was defined as the rate at which dP/dt_{max} and τ reached a maximum and minimum, respectively, during progressive increases in heart rate. We showed previously that hyperthyroidism significantly increases the critical heart rates for both dP/dt_{max} and τ.

The EC_{50} of dobutamine for LV dP/dt_{max} was determined by fitting log(dose)-transformed data to a sigmoidal relation with software from GraphPad.

Terbutaline Group

Additional animals were chronically instrumented so that we could examine the effects of β_2-adrenergic stimulation. One animal died suddenly after receiving thyroid hormone for 20 days. In the remaining three animals, the β_2-adrenergic agonist terbutaline was infused both before and after production of the hyperthyroid state. Incremental doses of terbutaline (15 min/dose) were infused over a dosing range of 25–300 ng $\cdot$ kg^{-1} $\cdot$ min^{-1}.

Thyroid Function Tests

Thyroid function tests were performed before the baseline experiment in the euthyroid state and before the terminal experiment (within 24 h of the last dose of T_4) in the hyperthyroid state. T_3 radioimmunoassay, T_4, and free T_4 levels were measured at each state.

Evaluation

Paired mean data were compared by Student's *t*-test. The effects of thyroid status, catecholamine dose, and β-blockade on hemodynamic and dimension variables were examined with repeated-measures ANOVA (SuperAnova, Abacus Concepts). When significant differences were found, group means were compared with contrasts. A value of $P < 0.05$ was considered significant. Unless specified, data are expressed as mean $\pm$ SD.

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Cardiac Failure in Other Species

Purpose and Rationale

Various species have been used to study experimental cardiac failure.

Breisch et al. (1984) studied the effects of pressure-overload hypertrophy in the left myocardium of young adult **cats**. Hypertrophy was induced by a 90 % constriction of the ascending aorta.

Genao et al. (1996) recommended dilated cardiomyopathy in **turkeys** as an animal model for the study of human heart failure.

Do et al. (1997) studied energy metabolism in normal and hypertrophied right ventricle of the **ferret** heart.

Wang et al. (1994) studied Ca^{2+} handling and myofibrillar Ca^{2+} sensitivity in **ferret** cardiac myocytes with pressure-overload hypertrophy.

Bovine hereditary cardiomyopathy was recommended as an animal model of human dilated cardiomyopathy by Eschenhagen et al. (1995).

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Hypertrophy of Cultured Cardiac Cells

Purpose and Rationale

Kojima et al. (1994), Komuro et al. (1990, 1991, 1993), and Yamazaki et al. (1993, 1994, 1996) described a method to induce hypertrophy of cardiomyocytes by mechanical stress in vitro.

Procedure

Primary cultures from cardiomyocytes are prepared from ventricles of 1-day-old neonatal Wistar Kyoto rats. According to the method of Simpson and Savion (1982), the cultures are treated for 3 days with 0.1 mM bromodeoxyuridine to suppress proliferation of nonmyocardial cells. Elastic culture dishes ($2 \times 4 \times 1$ cm) are made by vulcanizing liquid silicone rubber consisting of methylvinyl polysiloxane and dimethyl hydrogen silicone resin using platinum as a catalyst. The bottom of the disk is 1 mm thick, and it is highly transparent because of no inorganic filler in either component. Cells are plated in a field density of 1×10^5 cells/cm^2 in culture medium consisting of Dulbecco's modified Eagle's medium with 10 % fetal bovine serum. Mechanical stress on cardiac cells is applied by gently pulling and hanging the dish on pegs. A 10 % change in length of the dish results in an almost identical change in the length of the cell along a single axis (Komuro et al. 1990). Cardiocytes are stretched by 5 %, 10 %, or 20 %. Drugs, e.g., an angiotensin II receptor antagonist, are added 30 min before stretch.

For protein analysis, the silicone dishes are stretched for 24 h after 2 days of serum starvation and [^{3}H] phenylalanine (1 μCi/ml) is added for 60 min. At the end of each stress, the cells are rapidly rinsed four times with ice-cold phosphate-buffered saline and incubated for 20 min on ice with 1 ml of 5 % trichloroacetic acid. The total trichloroacetic acid-insoluble radioactivity in each dish is determined by liquid scintillation counting.

For the determination of mitogen-activated protein kinase, cardiomyocytes are lysed on ice and centrifuged. Aliquots of the supernatants of myocyte extracts are incubated in kinase buffer (25 mM/l Tris–HCl, pH 7.4, 10 mM/l $MgCl_2$, 1 mM/l dithiothreitol, 40 μM/l APT, 2 μCi [γ -^{32}P]ATP, 2 μM/l protein kinase inhibitor peptide, and 0.5 mM/l EGTA) and substrates (25-μg myelin basic protein). The reaction is stopped by adding stopping solution containing 0.6 %HCl, 1 mM/l ATP, and 1 % bovine serum albumin. Aliquots of the supernatant are spotted on P81 paper (Whatman), washed in 0.5 % phosphoric acid, dried, and counted.

For determination of*c-fos mRNA*, Northern blot analysis is performed.

Evaluation

Values are expressed as mean ± SEM. Comparisons between groups are made by one-way ANOVA followed by Dunnett's modified *t*-test.

Critical Assessment of the Method

The interesting approach to induce hypertrophy of cardiac cells in vitro has been used predominantly by one research group. Confirmation by other research groups including modifications of the mechanical procedures seems to be necessary.

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