Ribonucleic Acid Synthesis in Experimental Cardiac Hypertrophy in Rats

II. ASPECTS OF REGULATION

By Barry I. Posner, M.D., and Barry L. Fanburg, M.D.

ABSTRACT

The sequence of events which lead to increased RNA synthesis in the heart following aortic constriction was studied with the use of inhibitors of protein and RNA synthesis. Puromycin given during the first 4 hours after operation inhibited the increase in RNA labeling with [32P] H3PO4 that occurred after 4 hours of aortic constriction without inhibiting RNA labeling in sham-operated rats. Puromycin had no effect on the 82P labeling of the alpha-phosphate of AMP which suggests that the effect on labeling of RNA is not mediated by the lowering of precursor specific activity. The dose of puromycin used inhibited the labeling of heart muscle protein with 3H leucine. Parafluorophenylalanine had no selective inhibitory effect on the increase of RNA labeling in the hypertrophying heart. Actinomycin in doses which did not affect labeling in sham-operated rats diminished the increase in RNA labeling in the hypertrophying heart.

The most likely interpretation of these data is that, following aortic constriction, synthesis of protein is required for subsequent stimulation of RNA synthesis, and this protein may be dependent upon the synthesis of new RNA templates. Any early increased synthesis would be of a minority species of protein since there was no increase in amino acid labeling of total heart protein until 4 to 6 hours after aortic constriction.

The stimulation of RNA labeling by aortic constriction was unaffected by digitalis treatment. The pressure-time index did not correlate with the increased labeling of RNA.

ADDITIONAL KEY WORDS puromycin parafluorophenylalanine actinomycin D digoxin intraventricular pressures protein labeling radioactive labeling of heart RNA pressure-time index

In the preceding paper (1), we demonstrated that labeling of cardiac RNA is stimulated soon after constriction of the aorta and characterized the RNA synthesized subsequent to aortic constriction. The present communication concerns the possible regulatory factors in the production of this increased labeling. In particular, the effects of puromycin and actinomycin are evaluated, and comparisons are made with data from the literature on the regenerating liver. The increase of RNA labeling was also compared with the left ventricular pressure-time index in the same hearts.

METHODS

Animals.—Male albino rats obtained from the Charles River Laboratories were fed Purina chow without restriction and used when 180 to 220 g in weight except where otherwise indicated.

Chemicals.—The following chemicals were used: parafluorophenylalanine and puromycin (Nutritional Biochemical Company), [4,53H] leucine (New England Nuclear Corporation), actinomycin D1 (Merck, Sharp & Dohme Re-

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search Laboratory), [3H] actinomycin D, 3.38 c/mm, (Schwarz BioResearch, Inc.), and digitoxin (Wyeth Laboratories). Other chemicals used are noted in the preceding publication (1).

The operative procedure for constriction of the aorta as well as techniques of labeling, extraction, purification, fractionation, and measurement of RNA and AMP were described in the preceding publication (1).

Labeling of heart muscle protein.—[4,3H] Leucine, 0.3 /Ac/g body weight, was injected into the tail vein of the rats at various times after operation. Two hours later the rats were killed, and hearts were removed and quickly frozen on dry ice. The tissue was allowed to thaw partially and was minced with scissors and homogenized in 10 ml of 5% trichloroacetic acid. The homogenate was centrifuged at 1000 X g for 10 minutes at 0°C; the supernatant fluid was discarded. The sediment was mixed thoroughly in 10 ml of ice-cold 5% trichloroacetic acid containing L-leucine, 5 mg/ml, and the suspension was again centrifuged at 1000 X g for 10 minutes. The sediment was heated in 10 ml of 5% trichloroacetic acid at 90°C for 15 minutes. After centrifugation, the residue was treated successively with 20 ml of 95% ethanol, 10 ml of ether:ethanol:chloroform (1:2:1), 10 ml of ether, and 10 ml of acetone. The final residue was dried in a vacuum desiccator overnight to give a white powder which will be referred to as the "protein residue."

About 5 mg of the protein residue was weighed out in duplicate. After the addition of 0.5 ml of 88% formic acid to each sample, the suspension was heated in an oven at 100°C for 15 minutes to give a clear solution. This solution was allowed to cool and counted in vials containing 0.5 g of 2-5-diphenyloxazole (PPO) and 0.005 g of 1,4-bis-(2-(5-phenyloxazolyl) benzene (POPOP) in toluene:2-ethoxyethanol:2:1, in a Packard tricarb liquid scintillation counter. The counting efficiency for 4H leucine, under these circumstances, was about 8%.

Preparation and injection of actinomycin, parafluorophenylalanine, puromycin, and digitoxin.—All preparations for intravenous injections were dissolved in 0.9% NaCl. Parafluorophenylalanine could be dissolved at a concentration no higher than 50 mM. Puromycin HCl was administered slowly by vein unless otherwise specified. Digitoxin was dissolved in a mixture of ethyl alcohol:glycerin:distilled H2O (2.5:1.5:1) and was administered intramuscularly into the buttocks. The rats were anesthetized lightly with ether prior to each intravenous injection. Control rats received the same amount of the solvent as the animals treated with the test substance.

Measurement of intraventricular pressures.—Animals were anesthetized with ether. The liver was gently retracted through an abdominal incision, and a transdiaphragmatic puncture of the left ventricle was made with a no. 22 gauge stainless steel needle. Pressures were recorded with a Sanborn transducer (no. 267-BC) and recorder (2-channel direct writer no. 350-1100C), and animals were killed immediately afterward. When pressure recordings were unstable or technically unsatisfactory, the animal was discarded. Those hearts from which RNA was to be extracted were removed rapidly after the pressure measurements and frozen between slabs of dry ice.

Results

KINETICS OF LABELING OF TOTAL HEART PROTEIN

The incorporation of radioactive leucine was used to compare protein labeling of heart muscle of rats with aortic constriction and sham-operated rats at various times after

<table>
<thead>
<tr>
<th>Time after operation of introduction of label</th>
<th>No. of animals</th>
<th>No. of animals</th>
<th>Mean specific activity of protein residue (counts/min/mg) ± S.E.</th>
<th>% increase in specific activity (C/S—1) 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hours</td>
<td>5</td>
<td>5</td>
<td>118 ± 3</td>
<td>114 ± 9</td>
</tr>
<tr>
<td>6 hours</td>
<td>4</td>
<td>4</td>
<td>160 ± 11</td>
<td>121 ± 10</td>
</tr>
<tr>
<td>24 hours</td>
<td>5</td>
<td>4</td>
<td>167 ± 8</td>
<td>102 ± 6</td>
</tr>
<tr>
<td>48 hours</td>
<td>3</td>
<td>3</td>
<td>145 ± 10</td>
<td>98 ± 6</td>
</tr>
<tr>
<td>7 days</td>
<td>4</td>
<td>4</td>
<td>117 ± 10</td>
<td>73 ± 4</td>
</tr>
</tbody>
</table>

C = rats with aortic constriction; S = sham-operated rats.

Although the same leucine preparation was not used at all times recorded, the same preparation was used for injection of all rats at any one postoperation time. This may account for the variability in specific activity between different times studied.
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TABLE 1

Operation (Table 1). In the first 4 hours after operation, there was little difference in protein labeling. An increase of labeling of hypertrophying heart muscle was evident at 6 to 8 hours after operation; its extent gradually increased during the first 4 days after operation.

EFFECT OF PUROMYCIN

Effect on protein labeling.—The efficiency and duration of action of puromycin in the inhibition of heart muscle protein labeling were determined with the use of [3H] leucine. Table 2 shows that 25 mg of puromycin suspension given intraperitoneally in hourly injections during a 4-hour labeling period resulted in a 70% inhibition of the labeling of heart muscle protein. This compares with data obtained in a similar study by Gorski et al. (2). Comparable inhibition was effected by the intravenous administration at hourly intervals of puromycin in 10 mg-aliquots.

The duration of effectiveness of protein blockade by puromycin was very short (Table 2); i.e., when puromycin was given only 1 hour prior to a 2-hour labeling period with [3H] leucine, there was negligible inhibition of protein labeling.

Effect on RNA labeling.—The rats received [32P] H3PO4 4 hours after operation and 4 hours later were killed. Puromycin was given intravenously in a dose of 10 mg for each injection. When given every hour from the time of operation throughout the entire 8 hours of study, puromycin abolished the stimulation of RNA labeling which occurred in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specific activity (counts/min/mg protein)</th>
<th>% inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>225</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>270</td>
<td></td>
</tr>
<tr>
<td>25 mg (ip)</td>
<td>75</td>
<td>70%</td>
</tr>
<tr>
<td>5 mg (iv)</td>
<td>95</td>
<td>63%</td>
</tr>
<tr>
<td>10 mg (iv)</td>
<td>67</td>
<td>73%</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg (iv)</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>68</td>
<td>61%</td>
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<tr>
<td>Mean</td>
<td>79</td>
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</tr>
<tr>
<td>10 mg</td>
<td>72</td>
<td>59%</td>
</tr>
<tr>
<td>Mean</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

In Experiment 1, each rat received intravenous injection of 0.3 μc of [3H] leucine/g body weight at 0 and 2 hours and were killed at 4 hours. Puromycin was given either in a suspension (0.5 ml of 20 mg puromycin/ml in 0.4 w Na2HPO4-NaH2PO4, pH 7.4) intraperitoneally or in a solution (0.2 to 0.4 ml of 25 mg of puromycin/ml in 0.9% NaCl) intravenously at the indicated times. In Experiment 2, rats received only one injection of the above dose of leucine intravenously and were killed 2 hours later. Puromycin was given in a single injection of 10 mg at the indicated times. Protein was isolated and radioactivity determined as described in Methods.

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**Effect of Puromycin on Labeling of RNA**

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>Duration of treatment</th>
<th>No. of animals</th>
<th>Specific activity of RNA (counts/min/OD)</th>
<th>Total Specific activity of RNA (counts/min/OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>28S</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean ± 1 SE of control mean</td>
<td>Mean ± 1 SE of control mean</td>
</tr>
<tr>
<td>Sham</td>
<td>Control</td>
<td>3</td>
<td>317 ± 36</td>
<td>413 ± 54</td>
</tr>
<tr>
<td></td>
<td>0 to 8 hours</td>
<td>2</td>
<td>337 ± 2</td>
<td>635 ± 17</td>
</tr>
<tr>
<td>Constriction of aorta</td>
<td>Control</td>
<td>3</td>
<td>1030 ± 150</td>
<td>1392 ± 240</td>
</tr>
<tr>
<td></td>
<td>0 to 8 hours</td>
<td>4</td>
<td>434 ± 44</td>
<td>822 ± 53</td>
</tr>
<tr>
<td></td>
<td>4 to 8 hours</td>
<td>3</td>
<td>863 ± 33</td>
<td>1113 ± 17</td>
</tr>
<tr>
<td></td>
<td>0 time only</td>
<td>1</td>
<td>717 ± 16</td>
<td>1137 ± 32</td>
</tr>
<tr>
<td></td>
<td>0 to 2 hours</td>
<td>1</td>
<td>420 ± 61</td>
<td>680 ± 52</td>
</tr>
<tr>
<td></td>
<td>0 to 3 hours</td>
<td>1</td>
<td>575 ± 46</td>
<td>830 ± 42</td>
</tr>
</tbody>
</table>

Administration of [32P]H3PO4 and puromycin is described in the text and in Methods. The rats were killed at 8 hours after operation, and RNA was extracted and purified as noted in Methods. The determination of 28S and total RNA was previously described (1).

It is of interest that the labeling of the 28S RNA was inhibited by 19%. When puromycin was given at the time of operation only, there was essentially no inhibition of RNA labeling. However, when given at 0, 1, and 2 or 0, 1, 2 and 3 hours after constriction, the inhibition was of the same order as that when puromycin was given for the entire 8 hours.

It was of interest to determine whether puromycin affects RNA labeling by inhibiting nucleotide precursor labeling. Puromycin, 10 mg iv, was given hourly for 4 hours after operation, and rats were injected with 1.5 μc/g of [32P] H3PO4 4 hours after aortic constriction. Four hours later, the rats were killed, and the specific activities of both RNA and AMP derived from tissue ATP were determined. Total RNA labeling in puromycin-treated rats was inhibited 30 to 40% compared to untreated rats. Despite this change, there was no depression of AMP specific activity in treated rats. (Treated = 7,550, 10,800 counts/min/OD260; untreated = 7,700, 7,720 counts/min/OD260.)
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EFFECT OF ACTINOMYCIN ON LABELING OF HEART RNA

To determine if there is a differential effect of actinomycin on labeling of heart RNA in rats with aortic constriction as compared with sham-operated rats, both groups were treated with various doses of actinomycin following operation and during RNA labeling. As seen in Table 4, inhibition of RNA in sham-operated rats occurred only when total dosage of actinomycin administered intravenously is 10 µg or more per animal. At 5 µg per animal, there was essentially no inhibition of labeling of RNA from sham-operated rats whereas labeling of total and 28S RNA from rats with aortic constriction was inhibited 32 and 46%, respectively. At 20 µg of actinomycin per animal, both groups were inhibited to about the same extent. In both sham-operated rats and those with aortic constriction, 28S RNA is inhibited to a greater extent than total RNA. When given intraperitoneally to rats with aortic constriction, a dose approximately 10 to 15 times the intravenous dose of actinomycin is required for a similar inhibitory effect.

EFFECT OF PARAFLUOROPHENYLALANINE ON LABELING OF RNA

Although parafluorophenylalanine (240 µm-moles) given in divided doses over the 8-hour postoperative period produced a 20 to 30% lowering of specific activity of RNA obtained from rats with aortic constriction labeled during the 4- to 8-hour postoperative period, this inhibition of labeling was no more than that obtained with sham-operated rats.

EFFECT OF DIGITALIS ON RNA LABELING IN HYPERTROPHY

Digitalis has been found to have several

<table>
<thead>
<tr>
<th>Total dose of actinomycin</th>
<th>Type</th>
<th>No.</th>
<th>Specific activity of RNA (counts/min/OD)</th>
<th>% Inhibition of control</th>
<th>Mean ± 1 SD</th>
<th>% Inhibition of control mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>28S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>C</td>
<td>4</td>
<td>1075 ± 95</td>
<td>0</td>
<td>1428 ± 220</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>1</td>
<td>550</td>
<td>0</td>
<td>600 ± 60</td>
<td>0</td>
</tr>
<tr>
<td>1 µg</td>
<td>S</td>
<td>1</td>
<td>578 ± 96</td>
<td>46</td>
<td>584 ± 135</td>
<td>32</td>
</tr>
<tr>
<td>5 µg</td>
<td>S</td>
<td>3</td>
<td>420 ± 40</td>
<td>5</td>
<td>702 ± 142</td>
<td>0</td>
</tr>
<tr>
<td>10 µg</td>
<td>S</td>
<td>1</td>
<td>295</td>
<td>34</td>
<td>452 ± 31</td>
<td>31</td>
</tr>
<tr>
<td>20 µg</td>
<td>C</td>
<td>1</td>
<td>406</td>
<td>67</td>
<td>505 ± 51</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>1</td>
<td>190</td>
<td>64</td>
<td>342 ± 48</td>
<td>48</td>
</tr>
<tr>
<td>40 µg</td>
<td>C</td>
<td>1</td>
<td>130</td>
<td>87</td>
<td>230 ± 80</td>
<td>80</td>
</tr>
<tr>
<td>300 µg</td>
<td>S</td>
<td>1</td>
<td>375</td>
<td>65</td>
<td>540 ± 62</td>
<td></td>
</tr>
</tbody>
</table>

*Single intraperitoneal injection at time of operation.

In each experiment, 3 to 5 rats underwent either constriction of the aorta (C) or a sham operation (S) and were injected intravenously with actinomycin in four equally divided doses of 0.25 ml each at 0, 2, 4, and 6 hours post-operation. The sum of these 4 doses is recorded in the Table. Labeling with [3H]HATP (2 µCi/g body weight) was carried out at 4 hours after operation, and 4 hours later the rats were killed. RNA was isolated, purified, and fractionated by sucrose gradient centrifugation as described in Methods.


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effects on cardiac cellular and subcellular processes (5-7). In addition, it has been reported to inhibit induced cardiac hypertrophy (8). Thus, we thought it to be of interest to determine if digitalis can affect the increase of RNA labeling consequent to aortic constriction. Rats, at an initial body weight of approximately 150 g, were injected intramuscularly daily for 5 to 8 days with 0.1 mg digitoxin until they attained body weights of 180 to 220 g. Control animals received similar injections of digitoxin solvent. The last dose was given the morning of operation. Aortic constrictions were performed on both groups, and animals were labeled with [3H]HPO₄ as previously described during the 4 to 8 hour postoperative period. There was no difference between labeling of RNA in treated and control animals, and it is concluded that under the conditions described, digitalis has no effect on labeling of RNA in the hypertrophying heart.

EFFECT OF AORTIC CONstriction ON LEFT VENTRICULAR FbEssure MEASUREMENTS

Left ventricular pressures were recorded, and pressure-time indices were calculated as noted in Table 5. After aortic constriction and soon (1 to 2 hours) after operation, both the peak systolic pressure and pressure-time index were significantly elevated above values from sham-operated rats. They remained elevated to the same extent 24 hours after constriction, and by 7 days they were higher

| Time after constriction | Peak systolic pressure ± 1 cm Hg | Pressure-time index ± 1 min<sup>2</sup> Hg x sec | C
|-------------------------|---------------------------------|-----------------------------------------------|---
| 1 to 2 hours            | 121 ± 8 (6)                     | 172 ± 5 (8)                                   | 3.42 ± 0.18 (9) 4.35 ± 0.23 (9)
| 4 hours                 | 127 ± 3 (7)                     | 174 ± 9 (5)                                   | 3.4 ± 0.1 (7) 4.6 ± 0.3 (5)
| 8 hours                 | 152 ± 19 (10)                   | 152 ± 19 (10)                                 | 4.56 ± 0.15 (10)
| 24 hours                | 132 ± 5 (4)                     | 103 ± 6 (10)                                  | 3.81 ± 0.3 (4) 4.65 ± 0.15 (10)
| 7 days                  | 139 ± 4 (7)                     | 200 ± 14 (5)                                  | 3.63 ± 0.18 (7) 5.56 ± 0.47 (5)
| Normals                 | 127 ± 4 (8)                     | 3.71 ± 0.02 (6)                               |---

S = sham-operated rats; C = rats with aortic constriction.

Left ventricular pressures were recorded at times indicated after operation as described in Methods. Pressure-time index (9) was calculated by multiplying the area under an average left ventricular pressure curve (mm Hg x sec) by the heart rate (beats/min). The number of animals used at each time is noted in parentheses.

TABLE 5

Effect of Constriction on Left Ventricular Peak Systolic Pressure and Pressure-Time Index
Relation of Pressure-Time Index to Specific Activity of RNA

Sarnoff and associates (9), utilizing the isolated dog heart, have demonstrated a close correlation between the tension (pressure)'time index (mean systolic pressure times the duration of systole) and oxygen utilization; thus, the pressure-time index may be considered to be related to cardiac work. Therefore, recordings of left ventricular pressure were made in rats before they were killed, and extraction of RNA, and pressure-time indices were calculated. Figure 2 shows that, when individual hearts were extracted for RNA, there was no correlation between specific activity of total or 28S RNA and the pressure-time index.

In a further attempt to evaluate the possibility of correlation between RNA labeling and pressure-time index, groups of left ventricles from hearts with similar pressure-time indices were extracted for RNA in the presence and absence of sodium dodecylsulfate, and corrections were made for the specific activity of AMP. This evaluation further supports the absence of correlation between pressure-time index and early RNA labeling in the hypertrophying heart (Table 6).

Discussion

The administration of a suitable dose of puromycin inhibited the increase in RNA labeling consequent to aortic constriction without affecting RNA labeling in sham-operated rats. Furthermore, puromycin was given only within the first 4 hours after constriction, and the inhibition was complete when given within this period after constriction. Although puromycin may have other effects on cellular function, in primary effect it is on inhibition of protein synthesis (10-12). Labeling of heart protein with radioactive amino acid was inhibited by puromycin in the doses used in our studies. In addition, there was no inhibition in labeling of the alpha-phosphate of AMP by puromycin. Although another mode of action of puromycin through another end of action of puromycin.
cannot be excluded with certainty, it is most likely that puromycin inhibits the stimulation of RNA synthesis in the hypertrophying heart by inhibiting the synthesis of protein within the first 4-hour interval after aortic constriction. Since stimulation of labeling of total heart protein was seen only 4 to 6 hours after constriction, any protein whose synthesis may be stimulated in the 4-hour interval after operation probably would be small in quantity.

Recent studies by Nair et al. (13), in a system similar to ours, have demonstrated no change in RNA polymerase during the first several hours and maximum increase at 2 to 3 days after aortic constriction. Taken with our data, this suggests that any protein whose synthesis may be required early for increased RNA synthesis is not RNA polymerase itself. It is of interest that the major effect of puromycin is to prevent the stimulation of ribosomal RNA labeling. This raises the possibility that an early requisite protein may be a ribosomal protein which is rate limiting for RNA synthesis.

In experiments on regenerating liver, Tsukada and Lieberman (14) have shown that at 2 to 4 hours after partial hepatectomy the rise in RNA labeling is unusually susceptible to inhibition by parafluorophenylalanine. They have inferred that the synthesis of an intermediary protein which is not RNA polymerase plays an important role in the chain of events consequent to partial hepatectomy.

We have been unable to obtain results with parafluorophenylalanine comparable to those obtained with puromycin or those seen with parafluorophenylalanine in regenerating liver (15-17). Though this may suggest that early synthesis of a specific protein does not take place and that the effect of puromycin is through interference with some process other than protein synthesis, another explanation for our results would be the different mechanism of action of parafluorophenylalanine from that of puromycin in the inhibition of protein synthesis. For example, the phenylalanine residues in the early protein synthesized in the hypertrophying heart could be small in number or not critical to its function.

Actinomycin D, at a dose which did not affect RNA labeling in sham-operated rats, inhibited the increase in RNA labeling in hypertrophying hearts. Since there was no difference in uptake of actinomycin D between hearts of rats with aortic constriction and sham-operated rats, the actinomycin data suggest that the postulated early protein may be synthesized on a newly made template whose synthesis in turn is unusually sensitive to inhibition by actinomycin D. The synthesis of a minority species of RNA very soon after constriction may not be detected by the type of analyses undertaken in the present studies.

Intraventricular pressure increased very soon after aortic constriction. Nevertheless, there was a 4-hour lag before RNA labeling was increased (1). Though a close temporal correlation did not obtain, it was of interest to see if there was a correlation between the degree of increase in RNA labeling and the work of the heart. The data demonstrate no correlation between the extent of stimulation of RNA labeling and the pressure-time index (9). Since pressure-time index is a relatively crude measure of cardiac work, more detailed hemodynamic measurements are needed to evaluate the relationship between early mechanical and biochemical events in cardiac hypertrophy.

Acknowledgments

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