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# Troponin Release and Reversible Left Ventricular Dysfunction After Transient Pressure Overload

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## ABSTRACT

**BACKGROUND** The authors previously demonstrated that brief ischemia elicits cardiac troponin I (cTnI) release and myocyte apoptosis in the absence of necrosis. It remains uncertain whether other pathophysiological stresses can produce apoptosis and transient cTnI release without ischemia.

**OBJECTIVES** This study sought to determine whether a transient increase in left ventricular (LV) preload elicits cTnI release in the absence of ischemia.

**METHODS** Propofol-anesthetized swine (N = 13) received intravenous phenylephrine (PE) (300 μg/min) for 1 h to increase left ventricular end-diastolic pressure (LVEDP) to ~30 mm Hg. Serial cTnI and echocardiographic function were assessed for 24 h, and myocardial tissue was analyzed for apoptosis and necrosis.

**RESULTS** PE infusion increased systolic blood pressure from 137 ± 14 mm Hg to 192 ± 11 mm Hg (mean ± SD; $p < 0.001$) and increased LVEDP from 17 ± 2 mm Hg to 30 ± 5 mm Hg ($p < 0.001$). Myocardial flow measurements demonstrated no evidence of ischemia. Hemodynamics normalized rapidly after PE, but LV ejection fraction remained depressed (32 ± 21% vs. 58 ± 7%; $p < 0.01$) with normalization after 24 h (51 ± 16%; $p = 0.31$). Baseline transcoronary cTnI release was low (16 ± 20 ng/l) but increased to 856 ± 956 ng/l ($p = 0.01$) 1 h after LVEDP elevation. Circulating cTnI rose above the 99th percentile within 30 min and remained elevated at 24 h (1,462 ± 1,691 ng/l). Pathological analysis demonstrated myocyte apoptosis at 3 h (31.3 ± 11.9 myocytes/cm$^2$ vs. 4.6 ± 3.7 myocytes/cm$^2$; $p < 0.01$), that normalized after 24 h (6.2 ± 5.6 myocytes/cm$^2$; $p = 0.46$) without histological necrosis.

**CONCLUSIONS** Transient elevations of LVEDP lead to cTnI release, apoptosis, and reversible stretch-induced stunning in the absence of ischemia. Thus, preload-induced myocyte injury may explain many cTnI elevations seen in the absence of clinical signs or symptoms of myocardial ischemia. (J Am Coll Cardiol 2018;71:2906-16)
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Serum cardiac troponin (cTn) concentrations are currently the preferred diagnostic biomarker for the noninvasive detection of myocardial injury and are commonly used in conjunction with clinical signs of ischemia to diagnose myocardial infarction (1). Nevertheless, it has become clear that transient elevations in cTn levels frequently occur in the absence of ischemia in patients, as well as following physiological stresses such as dobutamine stress testing and marathon running in normal hearts (2-5). The increased clinical utilization of cTn measurements and development of high-sensitivity cTn assays has led to a substantial increase in the prevalence of patients presenting with elevations in cTn

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reflecting myocardial injury not related to an acute coronary syndrome (ACS) (6). Indeed, in some studies, more than one-half of the patients with elevated serum cTn concentrations do not have clinical evidence of myocardial ischemia or evidence of an acute coronary syndrome (7–9). Although some cTn elevations are due to myocardial injury from myocarditis, the vast majority remain unexplained.

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Excessive myocyte strain from elevated left ventricular (LV) filling pressures may be an important cause of irreversible myocyte injury in the absence of myocardial ischemia. This is supported by chronic elevations of cTn and B-type natriuretic peptide in heart failure and a variety of other fluid overload states (10). Previous in vitro studies have demonstrated that increased strain stimulates myocyte apoptosis, but whether this occurs in vivo is unclear (11). We previously demonstrated that elevating left ventricular end-diastolic pressure (LVEDP) to 25 mm Hg in the absence of ischemia leads to calpain-mediated cTnI degradation in the isolated rat heart (12). Although it is unclear whether apoptosis, cTnI release, and proteolytic cleavage of cTnI are causally related to one another, we recently demonstrated myocyte apoptosis and delayed cTnI release after 10 min of what had widely been held to be "reversible" ischemia (13). These findings raise the possibility that there may be other pathophysiological stimuli leading to apoptotic myocyte injury that explain cTn elevations in the many circumstances not associated with an ACS.

Accordingly, we increased LVEDP to 30 mm Hg for 1 h in closed-chest swine by increasing myocardial afterload with phenylephrine (PE). We assessed serial coronary venous as well as circulating cTnI levels, LV function, and myocyte apoptosis at times up to 24 h later. Because preload elevation can impede coronary flow (14,15), we excluded ischemia by assessing subendocardial flow with microspheres. Our results demonstrate that a transient 1 h elevation in preload is sufficient to stimulate myocyte apoptosis, elevate circulating cTnI for at least 24 h,

**ABBREVIATIONS AND ACRONYMS**

**ACS** = acute coronary syndrome

**CS** = coronary sinus

**cTn** = cardiac troponin

**dP/dt** = rate of rise of left ventricular pressure

**LV** = left ventricle/ventricular

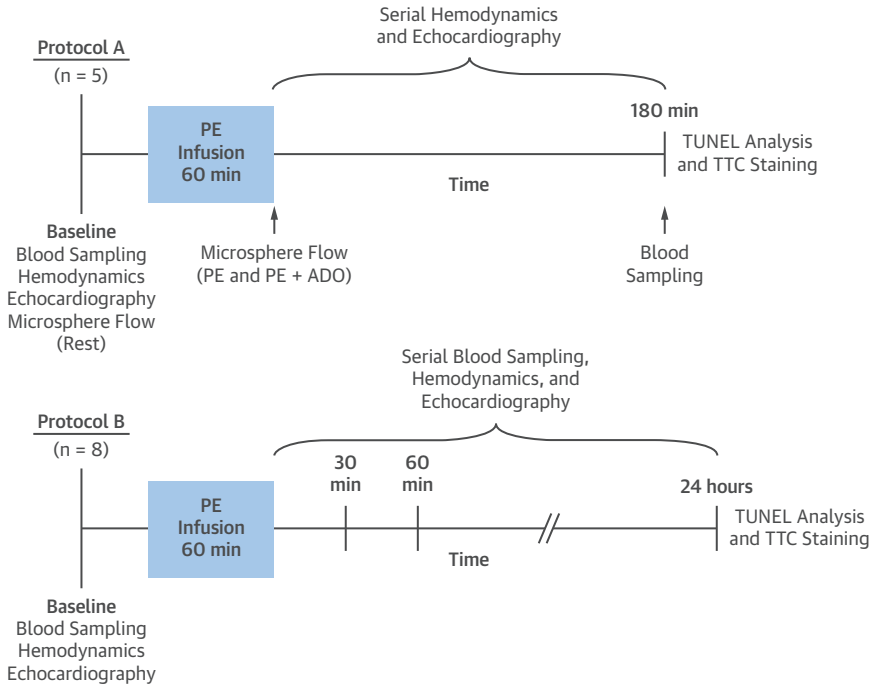
**LVEDP** = left ventricular end-diastolic pressure

**PE** = phenylephrine

**TTC** = triphenyltetrazolium chloride

**TUNEL** = terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling

**FIGURE 1 Experimental Protocol**




Following baseline data collection, swine were subjected to a 60-min intravenous infusion of PE (300 μg/min) and studied for 3 h (Protocol A; n = 5) or 24 h (Protocol B; n = 8). Serial blood sampling from the carotid artery and coronary sinus was performed at selected time points, along with assessment of hemodynamic parameters, left ventricular function, and myocardial perfusion. Following euthanasia, the heart was excised for gross assessment of infarction and histopathological quantification of myocyte apoptosis. ADO = adenosine; PE = phenylephrine; TTC = triphenyltetrazolium chloride; TUNEL = terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling.

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