increased during infancy to reach a nadir between 1 and 9 years of age. The marker increased again during early adolescence in both sexes, attaining its peak earlier in girls (11–13 years) than in boys (14–17 years). It subsequently decreased more rapidly in girls than in boys in later adolescence to reach a second, lower nadir in girls after the age of 15 years. In girls in late adolescence, serum CrossLaps concentrations were comparable to those previously reported for premenopausal adult women (3). The variation with age and sex shown by serum CrossLaps is similar to patterns previously observed for other markers of collagen formation and breakdown in children (1, 2, 5, 6) and reflects the pediatric growth curve. The timing of peak concentrations of serum CrossLaps in relation to chronological age coincided with the timing of peak height velocity in each sex on a population basis. No individual data were available for pubertal stage, height velocity, or bone mass acquisition in our study. As reported for other markers of collagen and bone turnover, at any age the range of serum CrossLaps values was wide, presumably reflecting individual variations in recent growth, pubertal progression, and bone modeling and remodeling.

In our study, nonfasting blood samples were collected between 900 and 1500. There is no published information on circadian variation of serum CrossLaps in infants or children. In adults, it has been demonstrated that circadian variation for serum CrossLaps is minimized by 24 h of fasting (7). This is not a viable option for children. In nonfasting adults, highest concentrations of serum CrossLaps occur overnight (as observed for other markers of bone collagen turnover), decreasing to relatively constant concentrations between 1000 and 1500 (7). The timing of collection of the blood samples in our study almost coincided with this optimal period and is appropriate to most routine clinical samples.

In summary, we have produced age- and sex-related 95% reference intervals for serum CrossLaps from birth to 19 years of age, together with log-transformed mean (and SD) values that will allow calculation of SD scores for use in future studies.

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References

Release Kinetics of Cardiac Troponin T in Survivors of Confirmed Severe Pulmonary Embolism, Margit Müller-Bardorff, Britta Weidtmann, Evangelos Giannitsis, Volkhard Kuroveski, and Hugo A. Katus* (Universitätsklinikum Lübeck, Medizinische Klinik II, Ratzeburger Allee 160, 23538 Lübeck, Germany; * author for correspondence: fax 49-451-5006437, e-mail katus@medinf.mu-luebeck.de)

Cardiac troponins may be increased in patients with confirmed pulmonary embolism (PE), even in the absence of significant coronary artery disease (CAD), and indicate increased risk for subsequent death (1). Cardiac troponin T (cTnT) correlates with the presence and degree of right-ventricular dysfunction (1, 2). In our recent study (1), 18 of 56 patients (32%) with PE had significant increases in cTnT. Eight of the nine patients with fatal outcome had increased cTnT. In the present study, we investigated all consecutive survivors of angiographically confirmed acute PE who developed cTnT ≥0.1 μg/L to evaluate cTnT time release in PE and to provide a rationale for an optimal blood-sampling protocol to improve risk stratification.

The study was approved by the local ethics committee of the University of Luebeck. All patients gave informed consent.

We enrolled nine consecutive patients with confirmed PE developing cTnT concentrations ≥0.1 μg/L, who survived the acute event and sampling period until normalization of cTnT concentrations. PE was suspected in the presence of an acute onset of symptoms such as dyspnea, pleuritic chest pain, syncope, hypotension, or shock and was confirmed by pulmonary angiography. The diagnostic work-up included transthoracic echocardiography, electrocardiography, blood-gas analysis, ventilation-perfusion scan, and coronary angiography. PE was graded according to the Goldhaber classification (3). PE patients were subsequently followed throughout their hospital stay. For controls, we studied six patients with confirmed acute coronary syndromes and microinfarction, defined as cTnT concentrations ≥0.1 μg/L with normal electrocardiograms and creatine kinase MB activity.

Standard therapy consisted of a parenteral bolus of 500 mg of acetylsalicylic acid and therapeutic doses of unfractionated heparin and β-blocker therapy adjusted according to activated partial thromboplastin time. Other medication was given at the discretion of the cardiologist on duty.

Serum samples were obtained on admission, every 4 h
for 24 h, and daily until discharge. At least four consecutive blood samples were obtained from each patient. cTnT concentrations were measured by a quantitative third-generation cTnT assay (ELECSYS 2010; Roche), which has a lower detection limit of 0.01 μg/L, discriminating cutoff of 0.1 μg/L (0.03 μg/L), and between-day imprecision (CVs; 11 analytical runs) of 20% at 0.015 μg/L, 10% at 0.03 μg/L, and 5% at 0.08 μg/L.

PE was graded as moderate in three and as severe in six of the patients [mean age, 65 years (SD, 15 years); six males, three females]. Onset of symptoms was 3–6 h before admission. Coronary angiography was performed in all patients and excluded coexistent significant CAD in eight patients. No intracoronary thrombus, abnormal TIMI (Thrombosis in Myocardial Infarction) flow, or impaired regional left-ventricular wall motion was observed. Thrombolytic therapy was administered to five patients, four of whom had massive PE. Median serial blood sampling was 40 h (interquartile range, 25–76 h).

One patient died of acute renal failure 10 days after the PE. In the six control patients with myocardial microinfarction, the diagnosis of CAD was confirmed by coronary angiography.

In acute PE, cTnT was increased in five of nine patients (56%) on admission and became positive in all within 8 h. After a median of 10 h, cTnT peaked to a median of 0.48 μg/L. cTnT ≥0.1 μg/L and ≥0.03 μg/L persisted for a median of 30 and 35 h, respectively. cTnT was detectable (>0.01 μg/L) for a median of 40 h after admission (Table 1; Fig. 1A).

In myocardial microinfarction, maximum cTnT ranged between 0.22 and 0.41 μg/L and differed from the distinct release curves seen in patients with nonreperfused or successfully reperfused acute myocardial infarction. cTnT remained increased for >120 h after admission and disclosed repeated discrete up and down slopes (Fig. 1B).

Our data suggest that cardiac troponins may be useful in PE, as they are in acute coronary syndromes (4, 5). The increased cTnT is believed to be the consequence of myocardial damage secondary to the acute rise of right-ventricular afterload attributable to myocardial ischemia and systemic hypoxemia (6, 7). In moderate to large acute myocardial infarction, cTnT requires 3 h to appear in blood after the onset of symptoms, remains increased for 10–14 days, and shows a characteristic pattern (early peak, persistent shoulder) owing to the compartmentation of cTnT in the myocardial cell (8, 9). In patients with microinfarction, release patterns are less distinct, showing lower maximum concentrations and lack of the typical monophasic early peak. In patients with coronary syndromes, repetitive up- and down-sloping of cTnT concentrations is suggestive of recurrent thromboembolic events (10).

The present study provides, for the first time, release curves for cTnT in survivors of angiographically defined PE in whom no coexistent significant CAD was detectable by means of coronary angiography. In contrast to findings in acute coronary syndromes, cTnT in patients with acute PE peaked after a median of 10 h, persisted at >0.1 μg/L (0.03 μg/L) for a median of 30 (35) h, and remained detectable (>0.01 μg/L) for a median of only 40 h after admission. Thus, the peak cTnT was lower than in acute myocardial infarction, it remained increased for a shorter time, and it did not show the multiple up and down slopes seen in microinfarction.

Our data suggest that the mechanism of myocardial damage and cTnT release in patients with significant PE is

### Table 1. cTnT release in PE patients.

| Patients with cTnT ≥0.1 μg/L on admission, n (%) | 5/9 (55.6) |
| Patients positive at 4 h, n (%) | 7/9 (77.8) |
| Patients positive at 8 h, n (%) | 9/9 (100) |
| Sampling period, h | 40 (25–76) |
| Peak cTnT, μg/L | 0.48 (0.24–0.66) |
| Time to peak, h | 10 (8–15) |
| Diagnostic window based on 0.1 μg/L cutoff, h | 30 (27–39) |
| Diagnostic window based on 0.03 μg/L, h | 35 (30–52) |
| Time of detectable cTnT (>0.01 μg/L), h | 40 (35–60) |

*Data given as medians with interquartile ranges (25th–75th percentiles) or as absolute numbers with relative frequencies.*
different from that in patients with acute coronary syndromes. Whether cTnT in PE patients originates from the cytosolic pool or from a different readily accessible cell pool or whether troponin release in PE is attributable to severe reversible or irreversible myocardial ischemia cannot be answered by our data and requires further studies. We propose, however, that early serial sampling is required to optimize risk stratification.

References