The nomogram technique for determining the prescription of death coming by the content of acid phosphatase in the muscle tissue

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Criminologists and medical examiners in practice are interested in the existence of reliable, stable criteria that would allow to unambiguously interpret certain post-mortem phenomena observed in the body, and which would allow to determine the age of death.
The aim of the study *was to study the postmortem patterns of acid phosphatase in muscle tissue (MT) of various types to improve the accuracy of determining the age of death.*
Materials and methods. *Determination of acid phosphatase content is performed in homogenates of myocardial, esophageal, diaphragm and intercostal muscles in the early postmortem period (PMP) (3-13 hours after death) in 30 human corpses. MT sampling was performed in the conditions of sectional biopsy with the use of special tools, preparation of MT homogenates – according to the standard method with subsequent determination of MT phosphatase content in MT homogenates by kinetic method.*
Results. *Analysis of postmortem changes in the content of acid phosphatase in MT depending on the time periods of the determining the age of death revealed that after 3 hours from the moment of death its content was the highest in a myocardium, the smallest – in MT of intercostal muscles (accordingly – 3,475±0,057 units/g and 2,662±0,028 units/g, p <0,001). The general pattern of acid phosphatase content in MT of different types was characterized by an increase in the content with increasing the age of death terms. In addition, the time series of changes in the acid phosphatase content obtained by us became the basis for substantiating the quantitative time dependences and constructing appropriate nomograms for forensic diagnosis of determining the age of death by the acid phosphatase content in MT.*
Conclusions. *It is proved that the content of acid phosphatase naturally (and nonlinearly) changed in all studied homogenates of MT, but the initial and final level of acid phosphatase, depending on the type of MT differs. In addition, the dynamics of changes in the content of acid phosphatase in the time period 3÷13 hours. from the moment of death, depending on the type of MT, also varies. The quantitative analytical and graphical dependences of the change in the content of acid phosphatase in MT in the early PMP revealed in the study allowed to substantiate the corresponding nomograms.*

Key words: *early postmortem period, prescription of death coming, muscle tissue, acid phosphatase*

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Technika nomogramu do określania czasu śmierci wynikającej z zawartości kwaśnej fosfatazy w tkance mięśniowej

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Kryminologów i lekarzy biegłych w praktyce interesuje istnienie wiarygodnych, stabilnych kryteriów, które pozwoliłyby jednoznacznie zinterpretować niektóre zjawiska pośmiertne obserwowane w organizmie, które mogą przybliżyć czas śmierci.
Celem pracy *było zbadanie pośmiertnych wzorców kwaśnej fosfatazy w tkance mięśniowej (MT) różnego typu w celu poprawy dokładności określania czasu zgonu.*
Materiały i metody*. Oznaczenie zawartości kwaśnej fosfatazy przeprowadza się w homogenatach mięśnia sercowego, przełyku, przepony i międzyżebrowej we wczesnym okresie pośmiertnym (PMP) (3-13 godzin po śmierci) w 30 zwłokach ludzkich. Pobieranie próbek MT wykonano w warunkach biopsji przekrojowej przy użyciu specjalnych narzędzi, preparując homogenaty MT – metodą standardową z późniejszym oznaczeniem zawartości fosfatazy MT w homogenatach MT metodą kinetyczną.*
Wyniki. *Analiza pośmiertnych zmian zawartości kwaśnej fosfatazy w MT w zależności od okresów określania wieku zgonu wykazała, że po 3 godzinach od śmierci jej zawartość była najwyższa w mięśniu sercowym, najmniejsza w MT mięśni międzyżebrowych (odpowiednio – 3,475±0,057 jednostek/g i 2,662±0,028 jednostek/g, p <0,001). Ogólny wzorzec zawartości fosfatazy kwaśnej w MT różnych typów charakteryzował się zwiększaniem zawartości wraz ze zwiększaniem wieku zgonu. Ponadto otrzymane przez nas szeregi czasowe zmian zawartości kwaśnej fosfatazy stały się podstawą do uzasadnienia ilościowych zależności czasowych i skonstruowania odpowiednich nomogramów do diagnostyki sądowej określania wieku zgonu przez zawartość fosfatazy kwaśnej w MT.*
Wnioski. *Udowodniono, że zawartość fosfatazy kwaśnej w sposób naturalny (i nieliniowy) zmieniała się we wszystkich badanych homogenatach MT, ale różne jest początkowe i końcowe stężenie fosfatazy kwaśnej w zależności od rodzaju MT. Dodatkowo ujawniono dynamikę zmian zawartości fosfatazy kwaśnej w okresie 3÷13 godzin od momentu śmierci, w zależności od typu MT. Przedstawione w badaniach ilościowe zależności analityczne i graficzne zmiany zawartości fosfatazy kwaśnej w MT we wczesnym PMP pozwoliły uzasadnić odpowiadające im nomogramy.*

Słowa kluczowe: *wczesny okres pośmiertny, czas śmierci, tkanka mięśniowa, kwaśna fosfataza*

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Criminologists and medical examiners in practice are interested in having reliable and stable criteria that would make it possible to interpret decisively some or other postmortem phenomena, which are observed in the organism, and at the same time enable forensic pathologists to approach the real values in determining the prescription of death coming (PDC) as much as possible and desirably as early as at the site of the event, with specification of this matter on autopsy in conditions of the department of forensic examination (FE) of corpses and laboratory sections [15]. The accumulation of acid phosphatase in muscle tissue (MT) leads to metabolic acidosis, is a marker of tissue hypoxia, metabolic disorders of intoxication [6,12,17-20]. The classical and firmly established accuracy in the determination of PDC within the early period provides an error of ±3 hours. The current development of medical science and practice requires from specialists a significant error decrease down to the level of ±1 hour and less, because high-technology abilities exist for it [5,7]. The development and subsequent introduction of new methods into practice for solving the above problem promises prospects of a reliable and accurate determination of criteria for death coming during the early period, objectivity and repeatability of results [2,3,4,8,15,21,22]. It is for this reason that the study of informative criteria for determining PDC is urgent and reasonable. On the other hand, the needs of law-enforcement agencies, who call for FE, particularly in terms of the accurate and rapid determination of PDC, currently require from forensic pathologists new approaches for solving the tasks they face.

The purpose of the research consisted in studying postmortem regularities of acid phosphatase (APh) content in different types of the muscle tissue (MT) for improving the accuracy of determination of PDC.

MATERIALS AND METHODS

The content of APh was determined in homogenates of the myocardial (MMH), oesophageal (OMH), diaphragm (DMH) and intercostal muscles (IMH) within the early postmortem period (PMP) (3-13 hours after the coming of death) on 30 human corpses.

MT was sampled in conditions of postmortem biopsy with use of special instruments; MT homogenates were prepared following the standard technique [10,11,14] with subsequent determination of APh content in MT homogenates by the kinetic method using the commercial test system of "DAC-SpectroMed" company (Moldova) and a Labline-80 biochemical analyzer (Austria) in accordance with their instructions. The findings were analysed statistically also with help of variation statistics and assessment of the normality of distribution and reliability of findings [13,16].

Information analysis of the pathometric sign (APh content) was made by calculation of its informativeness (I, bit) during each time interval as $I = -p*\log_2 p$, where p is the relation between the content of APh in MT homogenates after 3 hours and its content in the relevant postmortem time interval [9,10]. Presentation of revealed regularities in changes of APh content in each type of MT homogenates is provided by building dynamic lines with polynomials of different (2-5) stages and accuracy of reproduction $R^2>0.95$ [1,13]. The tabular nomogram was devised by dynamic extrapolation of polynomial dependencies with an interval of 30 minutes.

The studies were conducted following the basic regulations of *Ethical Principles for Medical Research Involving Human Subjects* approved by the Declaration of Helsinki (1964-2013), ICH GCP (1996), EEU Directive No. 609 (dated November 24, 1986), Orders of the Ministry of Health of Ukraine No. 690 (dated September 23, 2009), 944 (dated December 14, 2009) and 616 (dated August 03, 2012).

RESULTS AND DISCUSSION

The analysis of postmortem changes in the content of APh in MT depending upon time periods of PDC revealed that after 3 hours from the moment of death coming its highest content was in the myocardium, the least one being in MT of intercostal muscles (respectively, (3.475±0.057) and (2.662±0.028) U/g, $p<0.001$; tab. 1).

The level of content of APh in MMH during the analysed time intervals significantly ranged from (3.134±0.046) U/h in 3 hours after the coming of death to (2.757±0.025) U/h in 13 hours after death coming, reliably ($p<0.001$) differing in different time intervals of the early PMP. It should be noted that fluctuations of the absolute value of APh content were characterized by its increase within time intervals of 5÷9 hours. That is, as early as in 5 hours after the coming of death there was a reliable ($p<0.01$) increase of the above content up to (3.475±0.057) U/h, in 7 hours there was its reliable ($p<0.01$) re-increase up to (3.758±0.041) U/h, with a subsequent decrease of the content down to (3.616±0.037) U/h in 9 hours after death coming.

The dynamics of APh content in DMH during the analysed time intervals significantly ranged from (2.748±0.019) U/h in 3 hours after the coming of death to (4.449±0.032) U/h in 13 hours

Table 1. Levels and quantitative-analytical regularities in the content of acid phosphatase in different morphological types of the muscle tissue during the early postmortem period depending upon the prescription of death coming
Tabela 1. Poziomy i prawidłowości ilościowo-analityczne zawartości kwaśnej fosfatazy w różnych typach morfologicznych tkanki mięśniowej we wczesnym okresie pośmiertnym w zależności od czasu śmierci

Content (Y) of acid phosphatase and its informativeness	Postmortem time intervals (hours)					
	3	5	7	9	11	13
In homogenates of the myocardial muscles, MMH, U/g I_M = 0.999 bits	3.134±0.046	3.475±0.057	3.758±0.041	3.616±0.037	2.865±0.024	2.757±0.025
	0.000	0.165	0.315	0.239	0.118	0.162
	$Y_M = 0.033x^4 - 0.445x^3+1.85x^2-2.639x+4.329$; $R^2 = 0.992$					
In homogenates of the intercostal muscles, IMH, U/g I_R = 0.544 bits	2.409±0.027	2.662±0.028	3.083±0.041	3.216±0.033	2.797±0.046	2.601±0.029
	0.000	0.130	0.183	0.058	0.175	0.098
	$Y_R = 0.007x^5-0.097x^4+0.442x^3-0.762x^2+0.692x+2.127$; $R^2 = 1$					
In homogenates of the diaphragm muscles, DMH, U/g I_D = 0.758 bits	2.748±0.019	3.148±0.025	3.502±0.048	4.854±0.036	4.647±0.032	4.449±0.032
	0.000	0.275	0.138	0.340	0.060	0.045
	$Y_D = 0.006x^4 - 0.139x^3+0.856x^2-1.198x+2.977$; $R^2 = 0.951$					
In homogenates of the oesophageal muscles, OMH, U/g I_O = 0.717 bits	2.748±0.019	3.111±0.023	3.898±0.066	4.039±0.036	3.681±0.039	3.338±0.023
	0.000	0.158	0.260	0.049	0.122	0.128
	$Y_O = 0.033x^4 - 0.476x^3+2.209x^2-3.406x+4.384$; $R^2 = 0.997$					

after death coming, reliably (p<0.001) differing in different time intervals of the early PMP. That is, as early as in 5 hours after the coming of death there was a reliable (p<0.01) increase of the above content in DMH up to (3.148±0.025) U/h, in 7 hours there was its reliable (p<0.01) re-increase up to (3.502±0.048) U/h, and during subsequent time intervals the content of APh went on increasing; on the whole, during 10 hours of the early PMP the level of APh content in DMH increased by 1.6 times and was 182.0% of its initial value.

The level of APh content in OMH during the analysed time intervals significantly ranged from (2.748±0.019) U/h in 3 hours after the coming of death to (4.039±0.036) U/h in 9 hours after death coming, reliably (p<0.001) differing in different time intervals of the early PMP. Fluctuations of the absolute value of APh content were characterized by its increase within time intervals of 3÷9 hours. That is, as early as in 5 hours after the coming of death there was a reliable (p<0.01) increase of the above content up to (3.111±0.023) U/h, in 7 hours there was its reliable (p<0.01) re-increase up to (3.898±0.066) U/h and, having reached its maximum in 9 hours, later the content of APh decreased (versus 9 hours). It means that the level of APh content in OMH nonlinearly depended upon PDC terms.

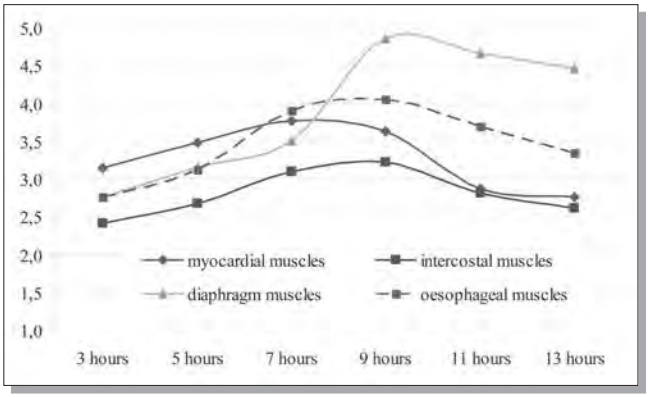

Figure 1. The comparative dynamics of the absolute content of acid phosphatase in different morphological types of the muscle tissue during the early postmortem period depending upon the prescription of death coming
Rycina 1. Porównawcza dynamika bezwzględnej zawartości kwaśnej fosfatazy w różnych typach morfologicznych tkanki mięśniowej we wczesnym okresie pośmiertnym w zależności od czasu śmierci

The level of content of APh in IMH during the analysed time intervals significantly ranged from (2.409±0.027) U/h in 3 hours after the coming of death to (3.216±0.033) U/h in 9 hours after death coming, reliably (p<0.001) differing in different time intervals of the early PMP. It should be noted that fluctuations of the absolute value of APh content were characterized by its increase within the time intervals of 3÷9 hours. That is, as early as in 5 hours after the coming of death there was a reliable (p<0.01) increase of the above content up to (2.662±0.028) U/h, in 7 hours there was its reliable (p<0.01) re-increase up to (3.083±0.041) U/h and, having reached its maximum in 9 hours, later the content of APh decreased. It means that the level of APh content in IMH nonlinearly depended upon PDC terms (fig. 1).

Thus, the common pattern of the content of APh in different types of MT was characterized by its rising with increasing terms of PDC; after all, the dynamic lines of APh content changes, which we obtained, became basic ones in substantiating quantitative temporal dependencies and constructing proper nomograms for forensic diagnosis of PDC by the content of APh in MT.

The quantitative dependencies between the content of APh and PDC, that we statistically justified, have the analytical form (polynomial stages 2-5) and their use enabled us to represent the revealed regularity and determine “intermediate” (between time intervals, p<0.01) values of APh content, thereby in its turn making it possible to increase the accuracy in diagnosing PDC.

Table 2. The tabular (top) nomograms for determining the prescription of the term of death coming by the content of acid phosphatase in the human muscle tissues with different localizations and morphological types
Tabela 2. Tabelaryczne (górne) nomogramy do określania czasu śmierci wynikającego z zawartości kwaśnej fosfatazy w tkankach mięśni ludzkich o różnej lokalizacji i typie morfologicznym

Prescription of coming		Content of acid phosphatase in homogenate of muscles (Y, U/g)							
Minutes	Hours	Myocardium, Y_M		Oesophagus, Y_O		Diaphragm, Y_D		Intercostal, Y_R	
1	2	3	$Y_M = 0.033x^4 - 0.445x^3+1.85x^2-2.639x+4.329;\ R^2 = 0.992$		$Y_O = 0.033x^4 - 0.476x^3+2.209x^2-3.406x+4.384;\ R^2 = 0.997$	5	$Y_D = 0.006x^4 - 0.139x^3+0.856x^2-1.198x+2.977;\ R^2 = 0.951$	6	$Y_R = 0.007x^5-0.097x^4 + 0.442x^3-0.762x^2+0.692x+2.127;\ R^2 = 1.0$
180	**3 hours**	**3.13**		**2.74**		**2.50**		**2.41**	
210	3 h 30 min.	3.13		2.73		2.56		2.45	
240	**4 hours**	**3.20**		**2.81**		**2.67**		**2.50**	
270	4 h 30 min.	3.30		2.95		2.81		2.58	
300	**5 hours**	3.42		3.13		2.99		2.67	
330	5 h 30 min.	3.53		3.33		3.19		2.78	
360	**6 hours**	**3.63**		**3.53**		**3.39**		**2.90**	
390	6 h 30 min.	3.70		3.71		3.61		3.01	
420	**7 hours**	**3.72**		**3.87**		**3.82**		**3.12**	
450	7 h 30 min.			3.99		4.02		3.22	
480	**8 hours**			**4.07**		**4.21**		**3.29**	
510	8 h 30 min.			4.10		4.38		3.32	
540	**9 hours**					**4.52**		**3.33**	
570	9 h 30 min.					4.63			
600	**10 hours**					**4.71**			
630	10 h 30 min.					4.76			
660	**11 hours**								
690	11 h 30 min.								
720	**12 hours**								
750	12 h 30 min.								
780	**13 hours**								

Besides, using methods of clinical informatics, we calculated informational values for dynamic changes in the content of APh for each time period and each type of MT. In particular, it was revealed that the total informativeness of determination of APh for diagnosing PDC by MT of the myocardium was I_{M-1} = 0.999 bits, by MT of the intercostal muscles I_{R-1} = 0.544 bits, by MT of the diaphragm I_{D-1} = 0.758 bits, by MT of the oesophagus I_{O-1} = 0.717 bits. It should be noted (tab.1) that the diagnostic value of determination of APh content depends upon the type of MT and the term of PDC (time interval of the early PMP). Thus, within the time interval up to 5 hours the most informative was the content of APh in MT of the diaphragm (I = 0.275 bits), during the time interval from 5 to 7 hours it was its content in MT of the myocardium (I = 0.315 bits), within the time interval from 7 to 9 hours the content of APh being of the highest diagnostic value (I = 0.340 bits). Proceeding from the above, the choice of the criterion "APh content in MT of the myocardium" is the most reasonable and preferred (a higher total diagnostic value), but in concrete tasks of FE one can use values of APh content in other types of MT as informative criteria.

In order to apply to practice of FE the regularities, revealed by us in the process of this investigation, and to introduce them into the work of medical examiners we constructed a graphic nomogram and made its simplified (traditional) tabular form (tab.2) for determining PDC by the level of APh in different types of MT. The presented nomograms make it possible to determine PDC by both a single diagnostic criterion (e.g., APh content in one type of MT) and several ones (APh content in different types of MT).

An example of forensic determination of PDC by the value of APh content in MT

In natural conditions of examination of a corpse the following morphological material (in the amount of 100 mg) was isolated by means of postmortem biopsy: MT of the myocardium, MT of the oesophagus, MT of the diaphragm, MT of the intercostal muscles. In conditions of biochemical laboratory the above MT fragments (100 mg) were homogenized in the physiological solution in the proportion of 20:1 (100 mg in 2.0 cm^3). After that, using a kit of reagents "DAC-SpectroMed", we prepared a working reagent; 2.0 µl of the supernatant fluid were added to 200 cm^3 of the working reagent and the resultant mixture was incubated during 5 minutes at t = 37.0°C, and then its optic density was measured thrice at a wavelength of 405 nm every minute. The activity of APh was calculated by the formula: APh = $_{\Delta}A \times 10 \times 743$, where $_{\Delta}A$ is the average value of the rate of change of optic density (per minute), 10 is the conversion factor for 1.0 g of MT, 743 is the conversion factor for U/g. The following values of the activity/content of APh were obtained: MMH_{APh} = 3.46 U/g, OMH_{APh} = 3.15 U/g, DMH_{APh} = 2.95 U/g, IMH_{APh} = 2.62 U/g. Proceeding from results of biochemical determination of APh activity in MT homogenates and using the nomogram (fig.1), we can conclude that PDC varies and corresponds to the following terms (See the tabular nomogram): 1) by APh content in MT of the myocardium – from 5 hours to 5 hours 30 minutes, 2) by APh content in MT of the oesophagus – also from 5 hours to 5 hours 30 minutes, 3) by APh content in MT of the diaphragm – from 4 hours 30 minutes to 5 hours, 4) by APh content in MT of the intercostal muscles – also from 4 hours 30 minutes to 5 hours.

Hence, by data of biochemical examination of APh content in different types of MT, PDC ranged from 4 hours 30 minutes to 5 hours 30 minutes from the moment of sampling of biopsy material. It should be noted that extrinsic factors (factors of the environment, where a corpse is after death), which can affect the dynamics of changes in the content of APh in different types of MT, were not taken into account.

Using morphological data from 30 corpses and PDC, which was verified in them before, we carried out inverse approbation of the nomogram technique for determination of PDC and revealed that the accuracy of determination for the term of PDC ranged within ±(0.5÷1.0) hours, with diagnostic errors of the first (α) and second (β) type being at the level of 10.00%.

CONCLUSIONS

It was proved that the content of APh in all examined MT homogenates changed regularly (and nonlinearly), but the initial and final levels of APh content differed depending upon the type of MT. Besides, the dynamics in changes of the content of APh within the time period of 3÷13 hours from the moment of death coming differed depending upon the type of MT too. The quantitative analytical and graphical dependences of the change in the content of APh in MT within the early PMP, revealed during the research, made it possible to substantiate relevant nomograms. Limitations for using the nomogram technique are as follows: PDC more than 10 hours and unknown conditions of the stay of a corpse after the coming of death (influence of environmental factors). Advantages of the technique consist in the integrity of biochemical examination of different types of MT and simplicity in interpretation of findings. The application of the nomogram technique for assessing PDC by APh content in MT makes it possible to improve the accuracy of diagnosis for terms of the coming of death up to 60 minutes.

Prospects of further researches regarding improvement in the accuracy of diagnosis of PDC are related to study of informativeness of other structural-biochemical markers of MT.

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